

Initial Submission

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

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4 Graduate Research Assistants

Personnel for these positions are *to be determined*. IRB amendments with detailed personnel information for these positions will be submitted as soon as personnel are identified.

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

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NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

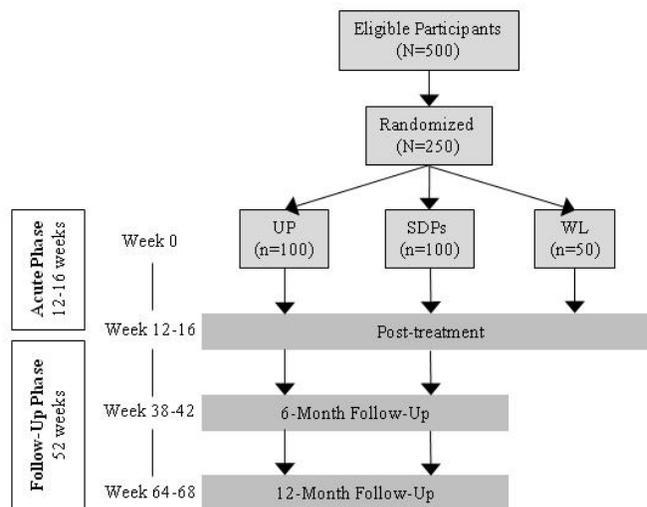
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will be immediately assigned to their choice of either UP or SDP treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 6 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 7th month of Year 1. Approximately 7 new participants will be recruited per month, with a total of 41 participants in Year 1, 84 participants in Years 2 and 3, and 41 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously

tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered their choice of treatment (UP or SDP) free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to four months for treatment at our Center. Patients in the waitlist condition will be assessed every 4 weeks during the course of the wait list. Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered the option of either SDP or UP treatment and treated clinically at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide

adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule

	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12 & 16	Post-WL or Post-Tx	6-Month and 12-Month Follow-Up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	*				
Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994)			* ²	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*			*	*
Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989)	*			*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*			*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*			*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*			*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*			*	*
Diagnosis Non-specific Self-report Measures					
Beck Depression Inventory (BDI-II; Beck et al., 1996)	*			*	*
Beck Anxiety Inventory (BAI; Beck et al., 1988; Beck & Steer, 1990; Steer, Ranieri, Beck, & Clark, 1993)	*			*	*
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*		* ²	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*		* ²	*	*
Potential Mediators of Treatment Change					
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		* ²	*	*
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		* ²	*	*
Behavioral Inhibition/ Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		* ²	*	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		* ²	*	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		* ²	*	*
Positive and Negative Affective Schedule - Global (PANAS-G; Watson, Clark, & Tellegen, 1988)	*		* ²	*	*
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		* ²	*	*
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		* ²	*	*
Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997)	*		* ²	*	*
Functional Impairment and Quality of Life					
Work and Social Adjustment Scale (WSAS; Marks, Connolly, & Hallam, 1973)	*			*	*
Rand-modified, Medical Outcomes Study 36-item Short-Form Health Survey (Rand-MOS-SF-36; Hays, Sherbourne, & Mazel, 1993)	*			*	*
Checklist of Emotional Avoidance Strategy Engagement (CEASE; Fairholme et al., under development)	*			*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilley & Borkevec, 2000)	* ¹				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*				
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			

1. Collected at the end of session two. 2. Collected at the start of session 1, and following sessions, 4, 8, and the last treatment session. Note: Treatment length will be 12 sessions for principal diagnoses of PD/A and 16 sessions for principal diagnoses of GAD, OCD, and SAD.

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer specific sections taken from an abbreviated version of the ADIS, focusing only on current

symptomatology (*Mini-ADIS-IV; Brown, Di Nardo, & Barlow, 1994*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift.

Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure,

Delgado, et al., 1989; Goodman, Rasmussen, & Price, 1999): The Y-BOCS interview is designed to assess the presence and severity of OCD symptoms, including assessment of insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 64-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference,

distress, resistance, and control. Items are scored on a 0 (none) to 4 (extreme) scale, yielding obsession and compulsion subscale scores (0-20) and a total score (0-40). The Y-BOCS interview has demonstrated excellent inter-rater reliability, good convergent validity, and is sensitive to treatment-related change (Goodman, Price, Rasmussen, Mazure, Fleischman, et al., 1989). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degree of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity

score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Beck Depression Inventory (BDI-II; Beck et al., 1996) and Beck Anxiety Inventory (BAI; Beck et al., 1988; Beck & Steer, 1990; Steer, Ranieri, Beck, & Clark, 1993): The BDI-II is a widely used measure assessing current depressive symptoms. It contains 21 items focusing on the levels of depressive symptoms over the past week. Participants are asked to circle the number next to the statement that best corresponds to how they felt over the past week. Scores range from 0 to 63, with higher scores indicating greater depressive symptoms. The BAI also contains 21 items scored in a similar way and focuses on common symptoms that are more unique to anxiety, such as somatic symptoms and certain cognitive symptoms.

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006).

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping

two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003): The ERQ is a 10-item self-report questionnaire that assesses individual differences in the dispositional tendency to employ two separate emotion regulation strategies – reappraisal and suppression. The scale has demonstrated high internal reliability and demonstrated strong convergent and discriminant validity (Gross & John, 2003).

Positive and Negative Affective Schedule – Global (PANAS-G; Watson, Clark, & Tellegen, 1988). The PANAS is a brief, reliable and valid measure of positive and negative affect. It consists of 20 feeling or emotion words (e.g., interested, upset, nervous). Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The PANAS-G has shown excellent convergent and divergent validity and is a widely used measure of state negative affect (Watson et al., 1988).

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 33-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions. For instance, the item “If I find myself getting mad, I try to calm myself down” from the TMMS, was changed to read “I try hard to calm myself down when I find myself getting angry.”

Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997). The ACS is a 42-item self-report measure designed to assess fear of loss of control when experiencing strong affective states. ACS subscales expand on the construct of fear of fear, including *fear of anxiety*, *fear of depression*, *fear of anger*, and *fear of strong positive affective states*. The ACS has demonstrated acceptable internal consistency, test-retest reliability, and convergent and divergent validity (Berg, Shapiro, Chambless, & Aherns, 1998; Williams et al., 1997).

Measures of Functional Impairment and Quality of Life

Work and Social Adjustment Scale (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item measure asking participants to rate the degree of interference caused by their symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a descriptive measure of subjective interference in various domains of living, and has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Rand-modified, Medical Outcomes Study 36-item Short-Form Health Survey (Rand-MOS-SF-36; Hays, Sherbourne, & Mazel, 1993): The Rand-MOS-SF-36 (Ware & Sherbourne, 1992) is a well-validated, comprehensive, self-administered instrument that is widely used in medical and psychiatric settings to provide a multi-dimensional assessment of mental and physical health-related status. The SF-36 measures 8 health related dimensions: physical functioning, bodily pain, role limitations due to physical health problems, general mental health, social functioning, energy/fatigue, and general health perceptions. The Rand-modified version of the SF-36 consists of identical items and scales but is scored differently and includes two factor analytically derived physical and mental health composite scores.

Checklist of Emotional Avoidance Strategy Engagement (CEASE; Fairholme et al., under development). The CEASE is a self-report questionnaire that was developed by the authors of the Unified Protocol assesses the frequency and severity of common emotional avoidance strategies (Barlow et al., 2008). It contains 68 checklist items of common emotional avoidance strategies followed by 6 supplemental questions which assess overall severity and interference due to use of these avoidance strategies. Some items were developed based on items of the Texas Safety Maneuvers Scale (TSMS; Kamphuis & Telch, 1998) and others were developed and agreed upon by a group of experts in the area of emotional disorders. Validation for the CEASE is currently ongoing.

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group,

1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). To reduce allegiance effects, therapists will be trained in either the UP or SDPs and will be dedicated to administering this treatment approach (UP or SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve a cut-off score of 5 (range 1 to 7) on all scales across at least 75% of sessions per case. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers

only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and p value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive their choice of the active treatments following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-

IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated \$50 for completion of posttreatment and follow-up assessments. Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

1. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
2. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
3. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
4. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
5. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who

had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.

6. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
7. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject’s medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any

recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Session recordings will be delivered only by hand or by United States Postal Service Certified Mail to the three expert raters included in the study staff, Gail Steketee, Michelle Craske, and Debra Hope. The expert raters will destroy the digital recordings after rating them.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 1:

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

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Personnel for these positions are *to be determined*. IRB amendments with detailed personnel information for these positions will be submitted as soon as personnel are identified.

4 Graduate Research Assistants

Personnel for these positions are *to be determined*. IRB amendments with detailed personnel information for these positions will be submitted as soon as personnel are identified.

1 Research Technician

The individual for this position is *to be determined*. An IRB amendment with detailed information for this position will be submitted as soon as personnel is identified.

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

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NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

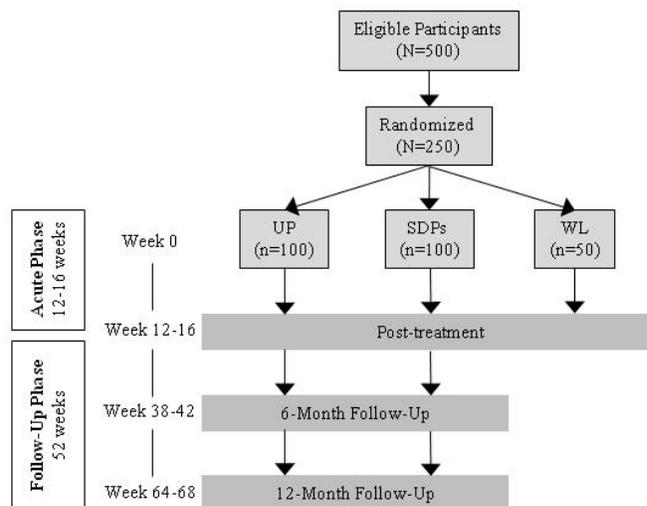
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



preliminary analyses, and the preparation of manuscripts.

Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures,

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously

tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to four months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic

treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule

	TIME OF ADMINISTRATION			
	Baseline	Each Session	Sessions 4, 8, 12 & 16	Post-WL or Post-Tx
Interview Based Assessments				
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	*			
Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994)			* ²	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Blitt, & Rucci, 2001; Williams, 1988)	*			*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*			*
Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989)	*			*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*			*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*			*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*			*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*			*
Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*
Diagnosis Non-specific Self-report Measures				
Beck Depression Inventory (BDI-II; Beck et al., 1996)	*			*
Beck Anxiety Inventory (BAI; Beck et al., 1988; Beck & Steer, 1990; Steer, Ranieri, Beck, & Clark, 1993)	*			*
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*		* ²	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*		* ²	*
Potential Mediators of Treatment Change				
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		* ²	*
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		* ²	*
Behavioral Inhibition/ Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		* ²	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		* ²	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		* ²	*
Positive and Negative Affective Schedule - Global (PANAS-G; Watson, Clark, & Tellegen, 1988)	*		* ²	*
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		* ²	*
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		* ²	*
Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997)	*		* ²	*
Functional Impairment and Quality of Life				
Work and Social Adjustment Scale (WSAS; Marks, Connolly, & Hallam, 1973)	*			*
Rand-modified, Medical Outcomes Study 36-item Short-Form Health Survey (Rand-MOS-SF-36; Hays, Sherbourne, & Mazel, 1993)	*			*
Checklist of Emotional Avoidance Strategy Engagement (CEASE; Fairholme et al., under development)	*			*
Potential Moderators of Treatment Outcome				
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)	* ¹			
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*			
Other Measures				
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*		

1. Collected at the end of session two. 2. Collected at the start of session 1, and following sessions, 4, 8, and the last treatment session. Note: Treatment length will be 12 sessions for principal diagnoses of PD/A and 16 sessions for principal diagnoses of GAD, OCD, and SAD.

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer

specific sections taken from an abbreviated version of the ADIS, focusing only on current symptomatology (*Mini-ADIS-IV; Brown, Di Nardo, & Barlow, 1994*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at out Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift.

Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure,

Delgado, et al., 1989; Goodman, Rasmussen, & Price, 1999): The Y-BOCS interview is designed to assess the presence and severity of OCD symptoms, including assessment of insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 64-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 4 (extreme) scale, yielding obsession and compulsion subscale scores (0-20) and a total score (0-40). The Y-BOCS interview has demonstrated excellent inter-rater reliability, good convergent validity, and is sensitive to treatment-related change (Goodman, Price, Rasmussen, Mazure, Fleischman, et al., 1989). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degree of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in

treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Beck Depression Inventory (BDI-II; Beck et al., 1996) and Beck Anxiety Inventory (BAI; Beck et al., 1988; Beck & Steer, 1990; Steer, Ranieri, Beck, & Clark, 1993): The BDI-II is a widely used measure assessing current depressive symptoms. It contains 21 items focusing on the levels of depressive symptoms over the past week. Participants are asked to circle the number next to the statement that best corresponds to how they felt over the past week. Scores range from 0 to 63, with higher scores indicating greater depressive symptoms. The BAI also contains 21 items scored in a similar way and focuses on common symptoms that are more unique to anxiety, such as somatic symptoms and certain cognitive symptoms.

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006).

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003): The ERQ is a 10-item self-report questionnaire that assesses individual differences in the dispositional tendency to employ two separate emotion regulation strategies – reappraisal and suppression. The scale has demonstrated high internal reliability and demonstrated strong convergent and discriminant validity (Gross & John, 2003).

Positive and Negative Affective Schedule – Global (PANAS-G; Watson, Clark, & Tellegen, 1988). The PANAS is a brief, reliable and valid measure of positive and negative affect. It consists of 20 feeling or emotion words (e.g., interested, upset, nervous). Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The PANAS-G has shown excellent convergent and divergent validity and is a widely used measure of state negative affect (Watson et al., 1988).

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 33-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions. For instance, the item “If I find myself getting mad, I try to calm myself down” from the TMMS, was changed to read “I try hard to calm myself down when I find myself getting angry.”

Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997). The ACS is a 42-item self-report measure designed to assess fear of loss of control when experiencing strong affective states. ACS subscales expand on the construct of fear of fear, including *fear of anxiety*, *fear of depression*, *fear of anger*, and *fear of strong positive affective states*. The ACS has demonstrated acceptable internal consistency, test-retest reliability, and convergent and divergent validity (Berg, Shapiro, Chambless, & Aherns, 1998; Williams et al., 1997).

Measures of Functional Impairment and Quality of Life

Work and Social Adjustment Scale – Self Rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item measure asking participants to rate the degree of interference caused by their symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a descriptive measure of subjective interference in various domains of living, and has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Rand-modified, Medical Outcomes Study 36-item Short-Form Health Survey (Rand-MOS-SF-36; Hays, Sherbourne, & Mazel, 1993): The Rand-MOS-SF-36 (Ware & Sherbourne, 1992) is a well-validated, comprehensive, self-administered instrument that is widely used in medical and psychiatric settings to provide a multi-dimensional assessment of mental and physical health-related status. The SF-36 measures 8 health related dimensions: physical functioning, bodily pain, role limitations due to physical health problems, general mental health, social functioning, energy/fatigue, and general health perceptions. The Rand-modified version of the SF-36 consists of identical items and scales but is scored differently and includes two factor analytically derived physical and mental health composite scores.

Checklist of Emotional Avoidance Strategy Engagement (CEASE; Fairholme et al., under development). The CEASE is a self-report questionnaire that was developed by the authors of the Unified Protocol assesses the frequency and severity of common emotional avoidance strategies (Barlow et al., 2008). It contains 68 checklist items of common emotional avoidance strategies followed by 6 supplemental questions which assess overall severity and interference due to use of these avoidance strategies. Some items were developed based on items of the Texas Safety Maneuvers Scale (TSMS; Kamphuis & Telch, 1998) and others were developed and agreed upon by a group of experts in the area of emotional disorders. Validation for the CEASE is currently ongoing.

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will

listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). To reduce allegiance effects, therapists will be trained in either the UP or SDPs and will be dedicated to administering this treatment approach (UP or SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve a cut-off score of 5 (range 1 to 7) on all scales across at least 75% of sessions per case. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-

pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to

answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive their choice of the active treatments following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

8. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
9. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
10. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
11. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
12. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
13. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
14. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the

safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the

occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.

- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 2:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB Amendment Request

Protocol number: 2349

PI name: David H. Barlow, PhD

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

Addition/ change to study investigators *(Human subjects training and COI documentation must be submitted with the amendment)*

Addition/change to funding *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

Addition/change to recruitment *(clean copy of the revised or new recruitment materials must be attached)*

Addition/change to the consent/assent form(s) - *(clean copy of each revised consent/assent form must be attached)*

Addition /change to recruitment numbers /study subjects *(description must include justification of revised sample size)*

Addition/ change to study design

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

Other – specify in text box below

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

1. We would like to request a change in assessment procedures. Specifically, we would like to administer the ADIS Super-Lite instead of the Mini-ADIS. The ADIS Super-Lite is a shorter version of the Mini ADIS designed for the

purposes of assessing change in current symptomatology over time. The ADIS Super-Lite will be administered according to the same assessment schedule as previously proposed for the Mini-ADIS (at pre-treatment, sessions 4, 8, 12, and 16; and at 6 and 12 months follow ups, except for individuals in the waitlist condition, as they will not receive follow-up assessments).

2. We would like to request the addition and/or modification of assessment measures. We would like to administer the Positive and Negative Affect Schedule – Expanded Form (PANAS-X) in place of the previously proposed Positive and Negative Affect Schedule – Global (PANAS-G) in order to provide a more updated and inclusive version of the measure. We also propose administering a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS), the Y-BOCS-II. Given our recent psychometric analysis of the Emotional Avoidance Strategies Inventory (EASI), we have made revisions to the wording of several of the items and would like to include this modified version. This modified version of the EASI contains one fewer item (total of 32 items instead of 33) and thus does not significantly alter the patient assessment burden. We also propose including several additional self-report measures as potential mediators of treatment change. These include the Southampton Mindfulness Questionnaire (SMQ) to assess the impact of mindfulness on treatment outcome; the Anxiety Subscale of the Cognition Checklist (CCL-A) to assess maladaptive thoughts associated with anxiety; the Savoring Beliefs Inventory (SBI) to evaluate the tendency to savor versus dampen positive emotions; two measures to assess sleep patterns, the Insomnia Severity Index (ISI) as well as selected questions from the Pittsburgh Sleep Quality Index (PSQI); and the Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q) to assess quality of life and overall well-being. Although we have added a number of short self-report measures, we do not anticipate any significant increase in overall patient burden, as we would like to omit 7 measures (see below), and as the ADIS Super-Lite requires significantly less time to administer than the Mini-ADIS, thus reducing the overall time of the study assessments.
3. Following pilot tests of the assessment measures and careful consideration of the participant burden, we propose omitting the following measures: the Beck Depression Inventory (BDI) and the Beck Inventory (BAI); the Anxiety Control Questionnaire-Revised (ACQ-R); the Emotion Regulation Questionnaire (ERQ); the Work and Social Adjustment Scale – Self-rated (WSAS-SR); the Rand Modified Medical Outcomes Study 36-Item Short Form Health Survey (Rand MOS SF-36), and the Checklist of Avoidance Strategy Engagement (CEASE).
4. We would like to amend the stated criteria for study therapist certification. Previously, we proposed that in order to achieve certification criteria, expert raters would review digitally recorded files of therapy cases delivered by study therapists, and that mastery was defined by receiving a cut-off score of 5 on a scale from 0-7. We now propose that certification criteria includes

achieving an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate." This change in certification criteria highlights the significance of both therapist adherence to the protocol and competence in delivering the protocol effectively as key factors essential for certification in treatment delivery.

5. In the initial IRB submission of the consent form, it was mistakenly reported that participants had approximately a 2/3 chance or greater of receiving immediate treatment, and a 1/3 chance of being allocated to the waitlist. In fact, participants have an 80% chance of receiving immediate treatment and a 20% chance of being placed on the waitlist. The text has been altered in the consent form to reflect this change.
6. In order to assess all participants on a similar time schedule, we have determined the necessity of administering assessment batteries to all study participants at 4, 8, 12, and 16 weeks during acute treatment. Previously, participants receiving treatment for panic disorder were not assessed at week 16, as the treatment protocol for panic disorder is completed within a 12-week time period. However, as treatment for social anxiety disorder, generalized anxiety disorder, and obsessive-compulsive disorder is completed within a 16-week time frame, all other participants are assessed at 16 weeks. To allow for consistent assessments across all participants, we propose that participants with panic disorder also be assessed 16 weeks after the start of their treatment. This change is reflected in the consent form on page 2.
7. We would like to report a change in personnel for the NIH/NIMH Program Officer for the grant. The current Program Officer is Jane L. Pearson.
8. We have made minor changes to the phone screen previously approved by the IRB. These changes were made to be more consistent with the information included in the consent form as well as to reflect updates to the research protocol.
9. In reviewing the research protocol for the purposes of this amendment, we made two additional minor changes to be consistent with previously approved amendments. The following changes were made to the research protocol for consistency: 1) participants in the waitlist condition will no longer chose which treatment they will receive; rather, the appropriate treatment will determined by their treating clinician and 2) study therapists will no longer be dedicated to either the UP or the SDPs, and will instead be certified and trained to administer both study treatments.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio

- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)
-

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significant affect the scientific integrity of the study.

Section IV: Attachments

- A. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.
- B. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature  Date 5/13/2011

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

 N/A **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

 Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

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3 Post-Doctoral Research Associates

Personnel for these positions are *to be determined*. IRB amendments with detailed personnel information for these positions will be submitted as soon as personnel are identified.

4 Graduate Research Assistants

Personnel for these positions are *to be determined*. IRB amendments with detailed personnel information for these positions will be submitted as soon as personnel are identified.

1 Research Technician

The individual for this position is *to be determined*. An IRB amendment with detailed information for this position will be submitted as soon as personnel is identified.

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

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NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

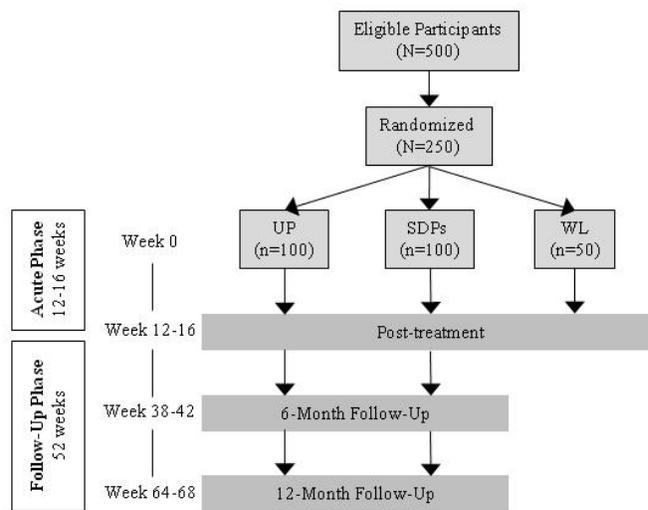
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will

be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et

al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

						6-Month and 12-Month Follow-Up
ANXIETY DISORDERS INTERVIEW SCHEDULE FOR DSM-IV LIFETIME VERSION (ADIS-IV-L; Di Nardo et al., 1994)						
ADIS Super Lite	*		*	*	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Blit, & Rucci, 2001; Williams, 1988)	*		*	*	*	*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	*	*
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Bejnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	*	*
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	*	*
Diagnosis Non-specific Self-report Measures						
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*		*	*	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*		*	*	*	*
Potential Mediators of Treatment Change						
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*	*
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	*	*
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*	*
Eysenck Personality Questionnaire Revised - Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	*	*
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		*	*	*	*
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		*	*	*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*		*	*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*	*
Functional Impairment and Quality of Life						
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*	*
Potential Moderators of Treatment Outcome						
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)	*					
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		*			
Other Measures						
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*				
1. Collected to determine eligibility for research study. 2. Also collected at the end of session 2. 3. Collected at session 4 only						

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain

a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown

to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006).

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping

two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 32-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions.

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, “Usually, when I have distressing thoughts or images” and continue with a mindfulness-related response, such as, “I am able just to notice them without reacting” and “I am able to accept the experience.” Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as

potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConnaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the

reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or

difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is

likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

15. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
16. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
17. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
18. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
19. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
20. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
21. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect,

or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.

- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



5/13/2011

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 3:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

- Addition/ change to study investigators** *(Human subjects training and COI documentation must be submitted with the amendment)*
- Addition/change to funding** *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*
- Addition/change to recruitment** *(clean copy of the revised or new recruitment materials must be attached)*
- Addition/change to the consent/assent form(s)** - *(clean copy of each revised consent/assent form must be attached)*
- Addition /change to recruitment numbers /study subjects** *(description must include justification of revised sample size)*
- Addition/ change to study design**
- Addition /change to study materials (e.g. surveys, questionnaires, etc.)** - *A copy of each of these new/revised materials must be attached*
- Other – specify in text box below**

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

1. We would like to update the information listed under study staff with following:
Post-doctoral Research Associates: Shannon Saur, Ph.D., and James Boswell, Ph.D.

Graduate Research Assistants: Johanna Thompson-Hollands, M.A, Jenna R. Carl, M.A., Kate Bentley, B.A.

Research Technician: Meghan Fortune, B.S.

Research Assistant: Amantia Ametaj, B.A.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significant affect the scientific integrity of the study.

Section IV: Attachments

- C. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.
- D. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature 

Date 8/29/11

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

David H. Barlow, PhD, Principal Investigator

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Assistant to PI

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Post-Doctoral Candidate in Clinical Psychology at Boston University

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James Boswell, Ph.D., Post-Doctoral Research Associate

Post-Doctoral Candidate in Clinical Psychology at Boston University

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1 Research Technician

Meghan Fortune, B.S., Research Technician

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Data and Safety Monitoring Board (DSMB)

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

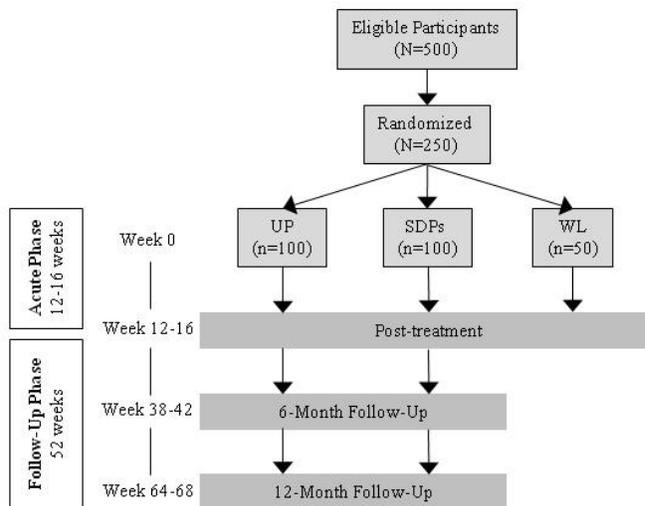
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any

patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous

algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	6-month Follow-up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
ADIS Super Lite	*		*	*	
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, et al., 1997)	*		*	*	
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*		*	*	
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*		*	*	
Potential Mediators of Treatment Change					
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		*	*	
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		*	*	
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	
Functional Impairment and Quality of Life					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)	* ²				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ³		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			

1. Collected to determine eligibility for research study.
2. Also collected at the end of session 2.
3. Collected at session 4 only

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006).

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 32-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions.

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, “Usually, when I have distressing thoughts or images” and continue with a mindfulness-related response, such as, “I am able just to notice them without reacting” and “I am able to accept the experience.” Items are rated on a 7-point

Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants’ “believability” in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual’s tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual’s score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002).

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment

condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator

other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or

requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study

will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

22. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
23. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
24. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
25. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
26. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
27. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
28. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and

serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.

3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject’s medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



5/13/2011

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 4:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

- Addition/ change to study investigators** *(Human subjects training and COI documentation must be submitted with the amendment)*
- Addition/change to funding** *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*
- Addition/change to recruitment** *(clean copy of the revised or new recruitment materials must be attached)*
- Addition/change to the consent/assent form(s)** - *(clean copy of each revised consent/assent form must be attached)*
- Addition /change to recruitment numbers /study subjects** *(description must include justification of revised sample size)*
- Addition/ change to study design**
- Addition /change to study materials (e.g. surveys, questionnaires, etc.)** – *A copy of each of these new/revised materials must be attached*
- Other – specify in text box below**

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

1. We would like to update the information listed under study staff with following:

Independent Evaluators: Matthew Gallagher, Ph.D., Michael Moore, Ph.D., and Jacqueline R. Bullis, M.A.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

- E. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.
- F. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature 

Date 8/29/11

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

David H. Barlow, PhD, Principal Investigator

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Amantia Ametaj, B.A., Research Assistant

Assistant to PI

(Address and phone same as PI)

3 Post-Doctoral Research Associates:

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James Boswell, Ph.D., Post-Doctoral Research Associate

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1 Research Technician

Meghan Fortune, B.S., Research Technician

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Doctoral Candidate in Clinical Psychology at Boston University

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Matthew Gallagher, Ph.D.

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

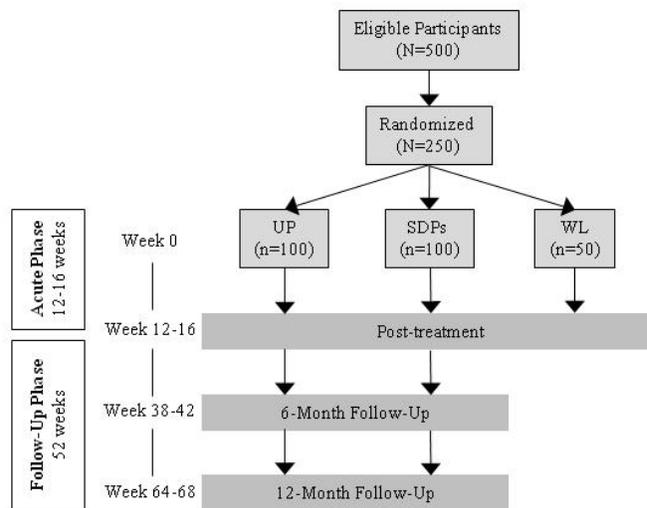
Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment

(outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa,

Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical

deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	6- or 12-Month Follow-up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
ADIS Super Lite	*		*	*	
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*		*	*	
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*		*	*	
Potential Mediators of Treatment Change					
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		*	*	
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		*	*	
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	
Functional Impairment and Quality of Life					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilley & Borkevec, 2000)	* ²				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ³		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			

1. Collected to determine eligibility for research study.
2. Also collected at the end of session 2.
3. Collected at session 4 only

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has

demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive

Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006).

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 32-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions.

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, “Usually, when I have distressing thoughts or images” and continue with a mindfulness-related response, such as, “I am able just to notice them without reacting” and “I am able to accept the experience.” Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In

addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the

second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConnaughy, Prochaska, & Velicer, 1983):

The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for

disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-

pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to

answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

29. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
30. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
31. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
32. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
33. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
34. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
35. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the

safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the

occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.

- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



5/13/2011

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 5:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

**BU Charles River IRB
Amendment Request**

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

Addition/ change to study investigators *(Human subjects training and COI documentation must be submitted with the amendment)*

Addition/change to funding *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

Addition/change to recruitment *(clean copy of the revised or new recruitment materials must be attached)*

Addition/change to the consent/assent form(s) - *(clean copy of each revised consent/assent form must be attached)*

Addition /change to recruitment numbers /study subjects *(description must include justification of revised sample size)*

Addition/ change to study design

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

Other – specify in text box below

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

1. We would like to request a change in the assessment procedures. Specifically, we would like to increase the frequency of administration for two of the self-report measures currently administered as part of this trial. We propose administering the ODSIS (Overall Depression Severity and Impairment Scale) and the OASIS (Overall Anxiety Severity and Impairment Scale) at all treatment sessions for participants in the two study treatment conditions. Currently it is being administered at pre-treatment, sessions 4, 8, 12, and 16; and at the 6 and 12 months follow up assessments. We believe that administering these measures more frequently will allow us to better explore the rate and pattern of change of anxiety and depression symptoms over the course of treatment. The measures are 5 items each (for a total of 10 items per administration) and, thus, we do not anticipate any significant increase in the overall patient burden.

2. We would like to revise one of the exclusion criteria. Currently participants are excluded from participation in the study for "current or recent (within 3 months) history of substance abuse or drug dependence." We propose maintaining this exclusion criterion with the exception of marijuana abuse as well as nicotine and/or caffeine abuse or dependence as these substances should not interfere with participation in treatment or require alternative treatment during participation in the study.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

G. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.

H. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature 

Date 8/29/11

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

David H. Barlow, PhD, Principal Investigator

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Amantia Ametaj, B.A., Research Assistant

Assistant to PI

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James Boswell, Ph.D., Post-Doctoral Research Associate

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1 Research Technician

Meghan Fortune, B.S., Research Technician

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

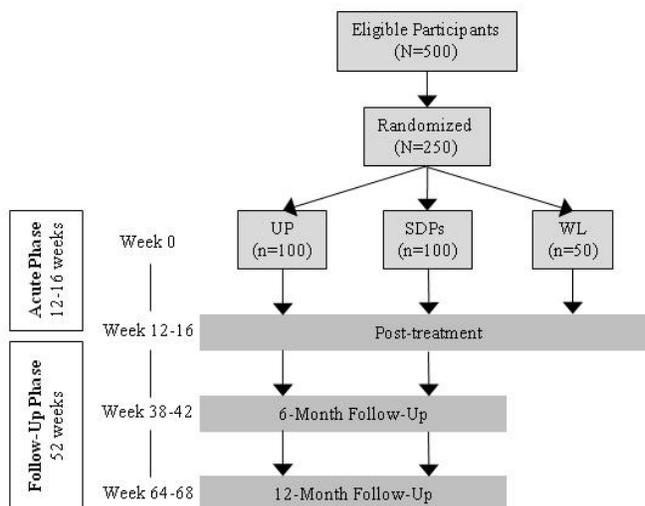
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures,

preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all

modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted,

instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	F
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
ADIS Super Lite	*		*	*	
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams,	*		*	*	
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*	*	*	*	
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*	*	*	*	
Potential Mediators of Treatment Change					
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		*	*	
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		*	*	
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Deville & Borkevec, 2000)	* ²				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ³		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
1. Collected to determine eligibility for research study.					
2. Also collected at the end of session 2.					
3. Collected at session 4 only					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's

symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test–retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 32-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions.

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, “Usually, when I have distressing thoughts or images” and continue with a mindfulness-related response, such as, “I am able just to notice them without reacting” and “I am able to accept the experience.” Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants’ “believability” in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual’s tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale

from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated

by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and

because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition,

to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlighting the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

36. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
37. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
38. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
39. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
40. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.

41. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
42. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an

unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the

annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



8/29/2011

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 6:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

Addition/ change to study investigators *(Human subjects training and COI documentation must be submitted with the amendment)*

Addition/change to funding *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

Addition/change to recruitment *(clean copy of the revised or new recruitment materials must be attached)*

Addition/change to the consent/assent form(s) - *(clean copy of each revised consent/assent form must be attached)*

Addition /change to recruitment numbers /study subjects *(description must include justification of revised sample size)*

Addition/ change to study design

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

Other – specify in text box below

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

1. We would like to request a change in the assessment procedures. Specifically, we would like to add three additional brief measures to the self-report assessment battery. We propose including the State Hope Scale (SHS) to assess the impact of hope and positive future expectations on treatment outcome, and the Adult Mental Health Continuum-Short Form (MHC-SF) to assess social, emotional and psychological well-being facets as an outcome of treatment. These two measures would be administered with our self-report battery at pre-treatment, sessions 4, 8, 12, and 16; and at the 6 and 12 months follow up assessments. In addition we propose including the Working Alliance Inventory – Short Form (WAI-SF) both the Client and Therapist self-report versions to assess the impact of the therapeutic alliance on treatment outcome. This measure would be administered as part of the self-report battery for assessments at session 4, 8 and 12. We do not anticipate the patient burden to increase since the measures are all very brief.
2. We would like to add two additional recruitment materials and modify previously IRB approved website content. We propose including a poster and postcard with the same content and design to be posted at local recruitment sites targeting prospective participants. We also propose a trifold brochure to be mailed to clinicians, therapists and mental health centers in the area which describes the study more in depth, allowing clinicians to be informed and refer patients to our study.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

- I. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.

- J. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature 

Date 12/23/2011

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

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Amantia Ametaj, B.A., Research Assistant

Assistant to PI

(Address and phone same as PI)

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Post-Doctoral Candidate in Clinical Psychology at Boston University

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1 Research Technician

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

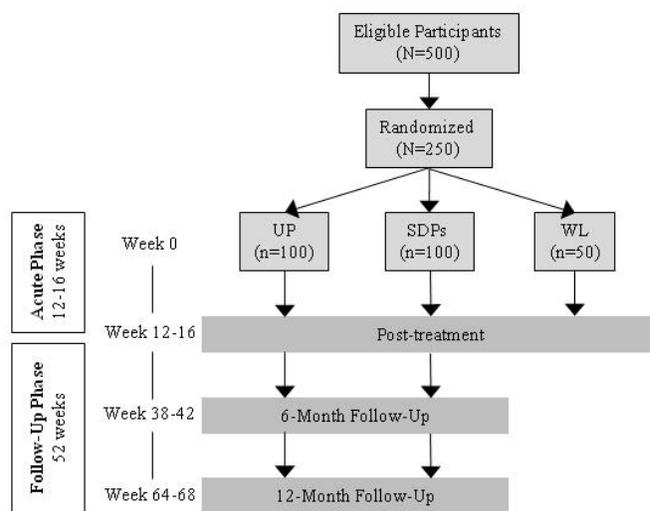
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments.

Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures,

These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients

randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the

assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures

	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	and 12-Month Follow-
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	*1				
ADIS Super Lite	*		*	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001)	*		*	*	*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	*
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	*
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	*
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*	*	*	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*	*	*	*	*
Potential Mediators of Treatment Change					
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	*
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	*
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		*	*	*
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		*	*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C. R., Sympson, S. C., Ybasco, F. C., Borders, T. F., Babyak, M. A., & Higgins, R. L., 1996)	*		*	*	*
Working Alliance Inventory – Short Form- Client Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q, Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF, Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof &	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)	*2				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		*3		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Working Alliance Inventory – Short Form-Therapist Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			*		
<p>1. Collected to determine eligibility for research study.</p> <p>2. Also collected at the end of session 2.</p> <p>3. Collected at session 4 only</p>					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test–retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008)

as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 32-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions.

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, “Usually, when I have distressing thoughts or images” and continue with a mindfulness-related response, such as, “I am able just to notice them without reacting” and “I am able to accept the experience.” Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants’ “believability” in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual’s tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the

second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConnaughy, Prochaska, & Velicer, 1983):

The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended

by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by

ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2

difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or

organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

43. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
44. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
45. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
46. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
47. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
48. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
49. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and

serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.

3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject’s medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



12/23/2011

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 7:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

Addition/ change to study investigators *(Human subjects training and COI documentation must be submitted with the amendment)*

Addition/change to funding *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

Addition/change to recruitment *(clean copy of the revised or new recruitment materials must be attached)*

Addition/change to the consent/assent form(s) - *(clean copy of each revised consent/assent form must be attached)*

Addition /change to recruitment numbers /study subjects
(description must include justification of revised sample size)

Addition/ change to study design

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

Other – specify in text box below

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

3. We would like to request a slight modification in the assessment procedures. Currently, participants are assessed at baseline using the ADIS Super-lite. Given a potential for a change in diagnoses when more than six weeks lapse between baseline and the initial CARD evaluation, we would like to conduct a more thorough evaluation, the Mini-ADIS-IV. Administration of the Mini-ADIS-IV is not expected to require more than 30 additional minutes compared to the Super-lite and is expected to occur infrequently.
4. We made a few minor changes to our recruitment materials with the main purpose of adding our new website and clarifying the language.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

- K. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.
- L. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature 

Date 12/23/2011

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

_____ **Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).**

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

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1 Research Technician

Meghan Fortune, B.S., Research Technician

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Independent Evaluators:

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Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

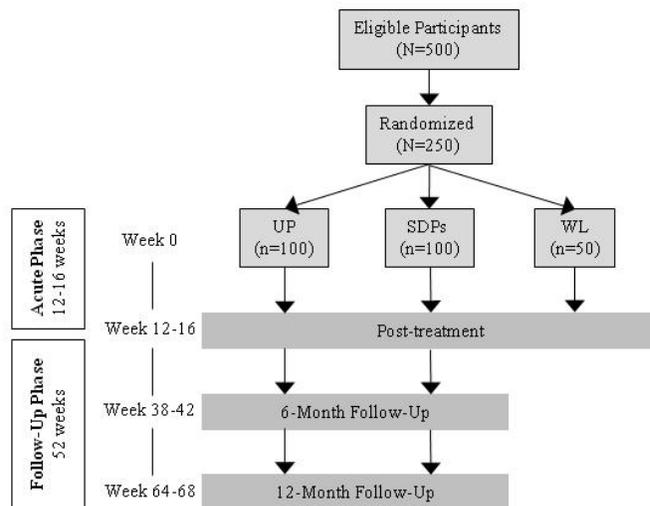
Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to

sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk,

2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data

Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants’ symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	and 12-Month Follow-
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
MINI ADIS	* ²				
ADIS Super Lite	*		*	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001)	*		*	*	*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	*
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirc, & Storch, 2006)	*		*	*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	*
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	*
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*	*	*	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*	*	*	*	*
Potential Mediators of Treatment Change					
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	*
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	*
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		*	*	*
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		*	*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C. R., Sympson, S. C., Ybasco, F. C., Borders, T. F., Babyak, M. A., & Higgins, R. L., 1996)	*		*	*	*
Working Alliance Inventory – Short Form- Client Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF, Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof &	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilley & Borkevec, 2000)	* ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Working Alliance Inventory – Short Form-Therapist Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			*		
1. Collected to determine eligibility for research study.					
2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline					
3. Also collected at the end of session 2.					
4. Collected at session 4 only					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994): ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (ADIS Super-Lite) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and

anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are

divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test–retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 32-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions.

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, “Usually, when I have distressing thoughts or images” and continue with a mindfulness-related response, such as, “I am able just to notice them without reacting” and “I am able to accept the experience.” Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants’ “believability” in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual’s tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a

broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given

additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to

determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such

treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

50. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
51. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
52. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
53. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
54. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
55. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.

56. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



3/2/2012

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 8:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB

Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

____ **Addition/ change to study investigators** *(Human subjects training and COI documentation must be submitted with the amendment)*

____ **Addition/change to funding** *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

____ **Addition/change to recruitment** *(clean copy of the revised or new*

recruitment materials must be attached)

___ **Addition/change to the consent/assent form(s)** - *(clean copy of each revised consent/assent form must be attached)*

___ **Addition /change to recruitment numbers /study subjects** *(description must include justification of revised sample size)*

___ **Addition/ change to study design**

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

___ **Other – specify in text box below**

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

5. We would like to request a change in the assessment procedures. Specifically, we would like to replace two existing assessment measures in the self-report assessment battery (the EASI and the ERSQ) with two other measures, as follows. The Multidimensional Experiential Avoidance Questionnaire (MEAQ) will be included to assess changes in several aspects of emotional avoidance as related to treatment outcome, and the Emotion Regulation Questionnaire (ERQ) will be used to assess cognitive and emotional regulation as an outcome of treatment. Additionally we propose adding the emotional awareness subscale of the Difficulties in Emotion Regulation Scales (DERS), comprised of 6 items, to assess changes in emotional awareness as related to treatment outcome. These measures would be administered with our self-report battery at pre-treatment, sessions 4, 8, 12, and 16; and at the 6 and 12 months follow up assessments. A total of only 19 additional items will be added to the assessment battery, overall. As a result, we do not anticipate a significant increase to patient burden.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

M. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.

N. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature  _____

Date 5/2/2012

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

__N/A__ Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

_____ Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

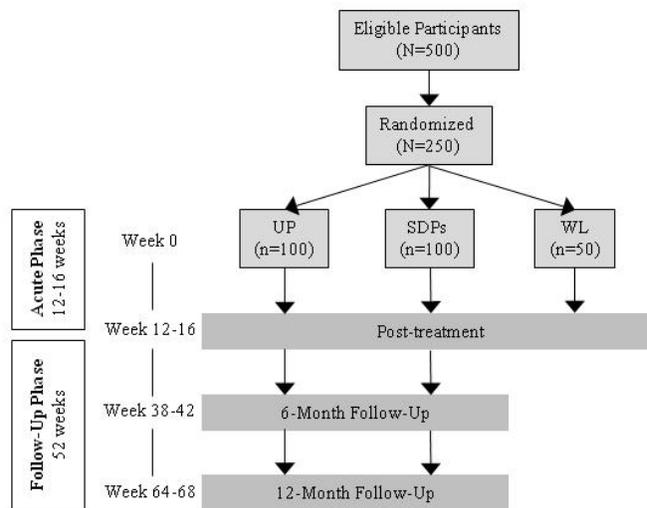
Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment

(outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa,

Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical

deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	and 12-Month Follow-
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	x ¹				
MINI ADIS	x ²				
ADIS Super Lite	x		x	x	x
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001)	x		x	x	x
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	x		x	x	x
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	x		x	x	x
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	x		x	x	x
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	x		x	x	x
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	x		x	x	x
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	x		x	x	x
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	x		x	x	x
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	x	x	x	x	x
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	x	x	x	x	x
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	x		x	x	x
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	x		x	x	x
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	x		x	x	x
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	x		x	x	x
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	x		x	x	x
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	x		x	x	x
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	x		x	x	x
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	x		x	x	x
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	x		x	x	x
Savoring Beliefs Inventory (SBI; Bryant, 2003)	x			x	x
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	x		x	x	x
Insomnia Severity Index (ISI; Morin, 1993)	x		x	x	x
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	x		x	x	x
State Hope Scale (SHS; Snyder, C. R., Sympson, S. C., Ybasco, F. C., Borders, T. F., Babyak, M. A., & Higgins, R. L., 1996)	x		x	x	x
Working Alliance Inventory – Short Form- Client Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			x		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	x		x	x	x
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF, Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof &	x		x	x	x
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)	x ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	x		x ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		x			
Working Alliance Inventory – Short Form-Therapist Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			x		
<p>1. Collected to determine eligibility for research study.</p> <p>2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline</p> <p>3. Also collected at the end of session 2.</p> <p>4. Collected at session 4 only</p>					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994); ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (ADIS Super-Lite) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test–retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral

avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency (alpha = .89), a significant correlation with the MAAS (r = .57), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress,

and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated

by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and

because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition,

to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlighting the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

57. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
58. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
59. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
60. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
61. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.

62. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
63. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an

unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the

annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



05/03/2012

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 9:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

Addition/ change to study investigators *(Human subjects training and COI documentation must be submitted with the amendment)*

Addition/change to funding *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

Addition/change to recruitment *(clean copy of the revised or new recruitment materials must be attached)*

Addition/change to the consent/assent form(s) - *(clean copy of each revised consent/assent form must be attached)*

Addition /change to recruitment numbers /study subjects
(description must include justification of revised sample size)

Addition/ change to study design

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

Other – specify in text box below

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

6. We made one minor changes to our recruitment materials with the main purpose of substituting the center's phone number with our new study cell telephone number.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

- O. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.
- P. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature 

Date 12/23/2011

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

 N/A **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

 Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

David H. Barlow, PhD, Principal Investigator

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Matthew Gallagher, Ph.D.

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. **Expected Duration of Study:** 5 years

7. **Description of Project.**

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

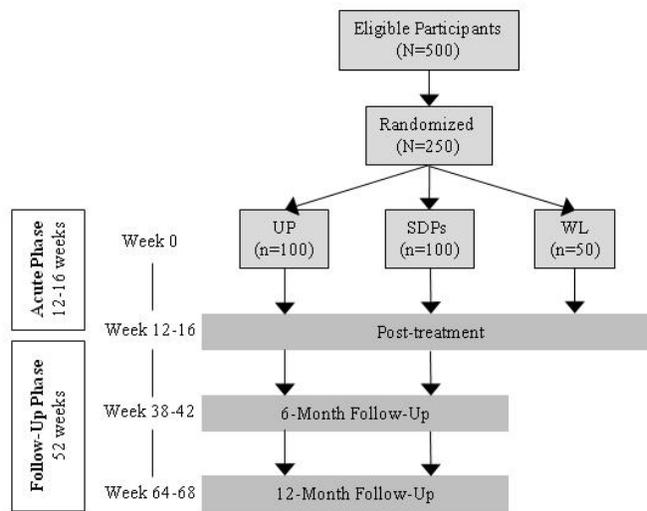
Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of

the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be

recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the

principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments

employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	and 12-Month Follow-
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	x ¹				
MINI ADIS	x ²				
ADIS Super Lite	x		x	x	x
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001)	x		x	x	x
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	x		x	x	x
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	x		x	x	x
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	x		x	x	x
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	x		x	x	x
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	x		x	x	x
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	x		x	x	x
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	x		x	x	x
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	x	x	x	x	x
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	x	x	x	x	x
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	x		x	x	x
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	x		x	x	x
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	x		x	x	x
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	x		x	x	x
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	x		x	x	x
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	x		x	x	x
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	x		x	x	x
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	x		x	x	x
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	x		x	x	x
Savoring Beliefs Inventory (SBI; Bryant, 2003)	x			x	x
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	x		x	x	x
Insomnia Severity Index (ISI; Morin, 1993)	x		x	x	x
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	x		x	x	x
State Hope Scale (SHS; Snyder, C. R., Sympson, S. C., Ybasco, F. C., Borders, T. F., Babyak, M. A., & Higgins, R. L., 1996)	x		x	x	x
Working Alliance Inventory – Short Form- Client Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			x		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	x		x	x	x
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF, Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof &	x		x	x	x
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)	x ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	x		x ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		x			
Working Alliance Inventory – Short Form-Therapist Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			x		
<p>1. Collected to determine eligibility for research study.</p> <p>2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline</p> <p>3. Also collected at the end of session 2.</p> <p>4. Collected at session 4 only</p>					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994); ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (ADIS Super-Lite) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test–retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral

avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency (alpha = .89), a significant correlation with the MAAS (r = .57), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress,

and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated

by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and

because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition,

to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlighting the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

64. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
65. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
66. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
67. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
68. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.

69. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
70. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject’s medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any

recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



05/03/2012

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 10:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB

Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

____ **Addition/ change to study investigators** *(Human subjects training and COI documentation must be submitted with the amendment)*

____ **Addition/change to funding** *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

____ **Addition/change to recruitment** *(clean copy of the revised or new*

recruitment materials must be attached)

Addition/change to the consent/assent form(s) - *(clean copy of each revised consent/assent form must be attached)*

Addition /change to recruitment numbers /study subjects *(description must include justification of revised sample size)*

Addition/ change to study design

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

Other – specify in text box below

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

7. We would like to update our active study staff by removing Michael Moore as one of the Independent Evaluators and changing the role of Kate Bentley from Graduate Research Assistant to Independent Evaluator. Also we would like to add two undergraduate research assistants, Dana Borkum and Julianne Wilner to the study roster.
8. We would like to add one questionnaire to our 6 month and 12 month follow-up assessments developed by our group to assess the utilization of treatment concepts and skills following the end of treatment. The questionnaire is comprised of 10 items and thus we do not expect it to add significantly to the patient burden.
9. We propose a clarification in the wording of our consent form under the heading "If you are asked to delay treatment." In an effort we would like to make this section more consistent with the previous section of the consent and to clarify procedures by stating, "We ask that you not start or actively receive any other type of treatment for anxiety or other psychological difficulties during your entire time participating in the study waitlist (the 16 week delay). If you or your non-CARD therapist think that additional therapy is necessary, it is very important that you discuss this with study staff first because it may interfere with the study. If this is the case, we

may have to remove you from the study. You and qualified study staff will discuss these issues before any action is taken. If you are taking any psychotropic medications (drugs for psychological problems such as anxiety or depression), we ask that you continue to take the current amount of the drug during your entire time participating in the study waitlist (the 16 week delay). If you and/or your doctor feel like a medication change is desirable, it is important that you discuss this issue with study staff as soon as possible. We also ask that you do not increase the use of any recreational drugs or alcohol while you are on the study waiting list (the 16 week delay)."

10. Lastly we would like to make a change to the description of the study IRB protocol under "G. Confidentiality" to make it more consistent with the corresponding section of the consent form. Please see IRB protocol for deletion of the sentence "Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area."

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed amendments pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

Q. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.

R. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature  _____

Date 8/8/2012

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

REQUEST FOR MODIFICATION RESPONSE FORM

PROTOCOL INFORMATION	
Protocol Number:	2349
Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Principal Investigator:	David H. Barlow, Ph.D., ABPP
Response to:	
<input type="checkbox"/> Initial Review <input type="checkbox"/> Continuing Review <input checked="" type="checkbox"/> Amendment	
<input type="checkbox"/> Other Event	

Instructions: Please respond to the IRB review by copying and pasting the comments from the IRB review letter onto this form. Add your response **DIRECTLY** below each of the IRB comments. Please include the following documents along with this form: 1) a copy of all revised documents in ‘Tracked Changes’ format or similarly notated to indicate what changes were made and 2) a “clean” copy of all revised documents.

Comments from the IRB:

Consent Form

1. The proposed wording changes the phrase “...it is very important that you discuss this with your CARD therapists first...” to “it is very important that you discuss this with study staff first...” Do you mean that the subject can discuss changes to his or her ongoing treatment with *any* member of your study staff or would the subject approach certain members of the study staff (e.g., CARD therapists)? If the latter is the case, please change the wording in the consent form to reflect this clarification

Our Response:

The wording was changed because it falls under the section entitled delayed treatment/ waitlist. Participants in this condition only interact with the research coordinator and the independent evaluators for the 16 weeks duration of the waitlist. The participants can note any changes in treatment or medication to the research coordinator or the independent evaluators so we would prefer to keep the more general term of study staff.

IRB Comment:

2. The IRB has removed the phrase “actively receive” and changed “additional therapy” to “additional or alternate therapy” in the consent form. Please review these modifications in the tracked changes version of the consent form attached to this e-mail.

Our response:

We have reviewed the modifications that the IRB has made to the consent form and we would like to state that it is important to retain the wording of “actively receive.” As stated in our IRB approved protocol and phone screen, delayed/waitlist participants are asked to not receive treatment for their symptoms of anxiety and depression for the duration of the waitlist. For this reason, we would like to make this stipulation as explicit as possible to the participants. In regards to the second change made by the IRB, we are in agreement with the change.

Principal Investigator’s Signature: _____



Date: __10/24/2012__

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be

included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

 N/A **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

 Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

David H. Barlow, PhD, Principal Investigator

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Amantia Ametaj, B.A., Research Assistant

Assistant to PI

(Address and phone same as PI)

3 Post-Doctoral Research Associates:

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Post-Doctoral Candidate in Clinical Psychology at Boston University

(Address and phone same as PI)

James Boswell, Ph.D., Post-Doctoral Research Associate

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(Address and phone same as PI)

Matthew Gallagher, Ph.D.

Post-Doctoral Candidate in Clinical Psychology at Boston University

(Address and phone same as PI)

4 Graduate Research Assistants:

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Doctoral Candidate in Clinical Psychology at Boston University

(Address and phone same as PI)

Jenna R. Carl, M.A., Graduate Research Assistant

Doctoral Candidate in Clinical Psychology at Boston University

(Address and phone same as PI)

Kate Bently, M.A., Graduate Research Assistant

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(Address and phone same as PI)

Jacqueline R. Bullis, M.A.

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(Address and phone same as PI)

1 Research Technician

Meghan Fortune, B.S., Research Technician

(Address and phone same as PI)

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Kate Bently, M.A.,

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Undergraduate Research Assistants

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Undergraduate Student at Boston University

(Address and phone same as PI)

Dana Borkum

Undergraduate Student at Northeastern University

(Address and phone same as PI)

Data and Safety Monitoring Board (DSMB)

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National Center for PTSD

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

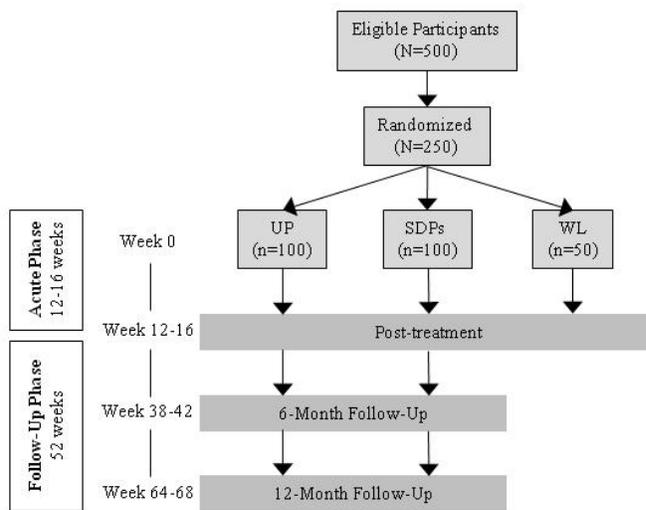
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will

be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	6-Month and 12-Month Follow-Up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	x ¹				
MINI ADIS	x ²				
ADIS Super Lite	x		x	x	x
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bit, & Rucci, 2001)	x		x	x	x
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	x		x	x	x
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	x		x	x	x
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	x		x	x	x
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	x		x	x	x
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	x		x	x	x
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	x		x	x	x
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Conolly, & Hallam, 1973)	x		x	x	x
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	x	x	x	x	x
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	x	x	x	x	x
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	x		x	x	x
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	x		x	x	x
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	x		x	x	x
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	x		x	x	x
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	x		x	x	x
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	x		x	x	x
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	x		x	x	x
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	x		x	x	x
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	x		x	x	x
Savoring Beliefs Inventory (SBI; Bryant, 2003)	x			x	x
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	x		x	x	x
Insomnia Severity Index (ISI; Morin, 1993)	x		x	x	x
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	x		x	x	x
State Hope Scale (SHS; Snyder, C. R., Simpson, S. C., Ybasco, F. C., Borders, T. F., Babyak, M. A., & Higgins, R. L., 1996)	x		x	x	x
Working Alliance Inventory – Short Form- Client Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			x		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	x		x	x	x
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF, Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof &	x		x	x	x
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilley & Borkevec, 2000)	x ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	x		x ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		x			
Treatment Skills Usage Questionnaire					x
Working Alliance Inventory – Short Form-Therapist Version (WAI-SF, Tracey, T.J., & Kokotovic, A.M., 1989).			x		
1. Collected to determine eligibility for research study.					
2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline					
3. Also collected at the end of session 2.					
4. Collected at session 4 only					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994); ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test–retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral

avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency (alpha = .89), a significant correlation with the MAAS (r = .57), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress,

and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle

Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 ,

standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and p value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more

current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A

total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

71. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
72. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
73. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
74. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.

75. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
76. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
77. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and

communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used

by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



08/08/2012

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 11:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB

Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

Addition/ change to study investigators *(Human subjects training and COI documentation must be submitted with the amendment)*

Addition/change to funding *(Stop here: with new funding usually a new protocol must be submitted rather than an amendment)*

Addition/change to recruitment *(clean copy of the revised or new*

recruitment materials must be attached)

Addition/change to the consent/assent form(s) - *(clean copy of each revised consent/assent form must be attached)*

Addition /change to recruitment numbers /study subjects *(description must include justification of revised sample size)*

Addition/ change to study design

Addition /change to study materials (e.g. surveys, questionnaires, etc.) – *A copy of each of these new/revised materials must be attached*

Other – **specify in text box below**

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

11. We would like to add three self-report questionnaires that assess symptoms specific to the patients' principal diagnoses of PD/A, Social anxiety disorder, OCD, and GAD. The three measures are PSWQ, APPQ and OCI-R. These measures would be administered during the following time points: baseline, post-treatment, 6 month follow-up, and 12 month follow-up. The measures are all very brief and thus we do not expect them to add significantly to the patient burden.
12. We propose placing an ad in a Hispanic/Latino newspaper to target enrollment of Hispanic individuals in our study. Currently we are not meeting the proposed enrollment numbers for this subgroup and would like to pursue more targeted recruitment. We like to place the ad in El Mundo Boston, and El Planeta or other Hispanic/Latino community newspapers. These aforementioned newspapers mentioned each has a readership that spans 30,000 readers in the metro Boston area.
13. In IRB Amendment 7 we proposed using the Mini-ADIS-IV instead of the full ADIS-Super-lite when more than 6 weeks lapse between a patient's ADIS-Lifetime assessment and the study baseline. We would like to revert back to using the ADIS-Super-lite if this time lapse occurs. The reason for this change is that the time lapse has occurred more frequently than

originally expected and the procedure has proven too burdensome for our patients and IEs. Additionally the payoff of slightly more rigorous dimensional ratings has not proved justifiable since we will not be using this information for the final study analyses.

14. Lastly, we would like to add an exclusion criterion which has been a long-standing CARD rule of thumb. In order to receive treatment at our center, patients are asked to discontinue therapy for their anxiety and depression symptoms so as to minimize receiving conflicting information. We would like to make this rule more explicit by adding it as an exclusion criterion to our protocol.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed changes pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

S. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a "track changes" of the revised protocol.

T. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature  _____

Date 11/27/2012

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

 N/A **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

 Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

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NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

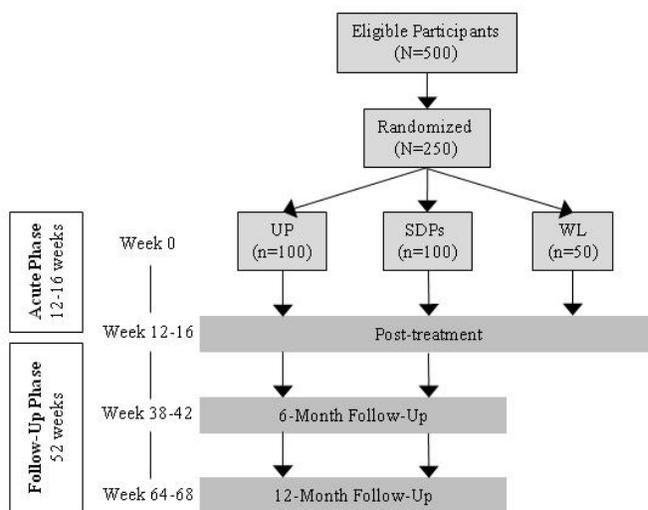
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will

be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	6-Month and 12-Month Follow-Up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
MINI ADIS	* ²				
ADIS Super Lite	*		*	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	*		*	*	*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	*
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	*
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	*
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*	*	*	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*	*	*	*	*
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994; 1995)	*			*	*
Obsessive-Compulsive Inventory-Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	*			*	*
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	*			*	*
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	*
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		*	*	*
Eysenck Personality Questionnaire Revised-Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	*		*	*	*
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Symson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (DeVilly & Borkevec, 2000)	* ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		

1. Collected to determine eligibility for research study.

2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline

3. Also collected at the end of session 2.

4. Collected at session 4 only

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994); ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCI; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation

(BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point

Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory

(WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for

supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-

pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to

answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinue psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or

active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is

likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

78. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
79. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
80. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
81. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
82. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
83. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
84. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging

inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.

- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



08/08/2012

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 12:

IRB Office Use Only

Date submitted _____

FB _____ Exp. _____

BU Charles River IRB

Amendment Request

Protocol number: 2349

PI name: David H. Barlow

An amendment is required for any changes made to the IRB protocol. Federal Regulations and Institutional Policy require that IRB approval be obtained PRIOR to making any amendments or changes to an approved IRB protocol except when the change is necessary to eliminate immediate harm to subjects. The IRB will inform you in writing when the amendment has been approved and no changes can be made to the research until that notification has been received.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study WILL NOT CHANGE. Previously approved versions of the consent forms should be archived and only the newly approved versions should be used.

Section I. Amendment Type *(check all that apply)*

Addition/ change to study investigators *(Human subjects training and*

COI documentation must be submitted with the amendment)

Addition/change to funding *(Stop here: with new funding usually a new*

protocol must be submitted rather than an amendment)

Addition/change to recruitment *(clean copy of the revised or new*

recruitment materials must be attached)

___ **Addition/change to the consent/assent form(s)** - *(clean copy of each revised consent/assent form must be attached)*

___ **Addition /change to recruitment numbers /study subjects** *(description must include justification of revised sample size)*

___ **Addition/ change to study design**

___ **Addition /change to study materials (e.g. surveys, questionnaires, etc.)** – *A copy of each of these new/revised materials must be attached*

___ **Other – specify in text box below**

Section II: Amendment Description. In the text box below provide a **detailed** description of the proposed changes to the protocol and consent. Whenever possible specify changes from XXX to YYY and state the corresponding Section(s) of the approved IRB protocol.

15. We would like to update our study staff section by removing Dana Borkum and adding C. Alexander Brake and Alexandra Convertino undergraduate and masters research assistants.

Section III: Change in risks to Subjects: In the text box below indicate whether the proposed amendment represents

- Any new, previously unidentified risks to subjects
- Any changes to previous risks or risk/benefit ratio
- Any changes that will require informing or re-consenting subjects (and if so what is the plan for doing this)

We do not believe that the proposed changes pose any new, previously unidentified risks to subjects or significantly affect the scientific integrity of the study.

Section IV: Attachments

- U. **Revised Protocol:** Attach a revised updated version of the IRB protocol with the changes/revisions highlighted or submit a “track changes” of the revised protocol.

V. **Additional Attachments** – Attach all additional attachments (as indicated in Section I of this form). All attachments must be submitted with this Amendment request. Failure to submit necessary attachments will result in a delay in processing this amendment.

PI printed name David H. Barlow

PI signature  _____

Date 1/11/2013

If PI is a student: Printed name of Faculty Advisor _____

Faculty Advisor signature _____ Date _____

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

David H. Barlow, PhD, Principal Investigator

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Amantia Ametaj, B.A., Research Assistant

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3 Post-Doctoral Research Associates:

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Matthew Gallagher, Ph.D.

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Jacqueline R. Bullis, M.A.

Doctoral Candidate in Clinical Psychology at Boston University

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1 Research Technician

Meghan Fortune, B.S., Research Technician

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Undergraduate Student at Boston University

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C. Alex Brake

Masters Student at Boston university

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Undergraduate Student at Northeastern University

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Data and Safety Monitoring Board (DSMB)

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify

training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

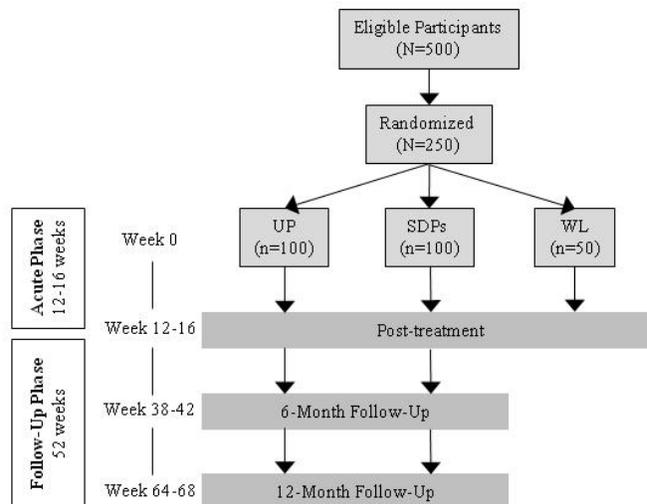
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



preliminary analyses, and the preparation of manuscripts.

Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures,

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient

flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of

the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for

the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	6-Month and 12-Month Follow-Up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
MINI ADIS	* ²				
ADIS Super Lite	*		*	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	*		*	*	*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	*
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	*
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Conolly, & Hallam, 1973)	*		*	*	*
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*	*	*	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*	*	*	*	*
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994; 1995)	*			*	*
Obsessive-Compulsive Inventory-Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	*			*	*
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	*			*	*
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	*
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		*	*	*
Eysenck Personality Questionnaire Revised-Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	*		*	*	*
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Symson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilley & Borkevec, 2000)	* ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		

1. Collected to determine eligibility for research study.

2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline

3. Also collected at the end of session 2.

4. Collected at session 4 only

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994); ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCI; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation

(BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point

Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory

(WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for

supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-

pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to

answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinue psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or

active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is

likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

85. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
86. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
87. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
88. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
89. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
90. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
91. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging

inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.

- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



1/11/2013

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 13:

IRB Office use only Date submitted _____ Exp. Date _____ FB _____ Exp. _____

**BU Charles River IRB
Amendment Request Form**

This form is to be completed when a change (amendment) is requested to an IRB-approved study. **NOTE:** All changes must be approved by the IRB **PRIOR** to implementation.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study **WILL NOT CHANGE**. Previously approved versions of the consent forms should be archived as they are no longer valid and only the newly approved versions should be used.

Study Staff Changes: Changes to study staff can be made by submitting the Study Staff Amendment Form. This form is located on the IRB website at: <http://www.bu.edu/irb/>.

SECTION A: PROTOCOL AND CONTACT INFORMATION

Protocol Number:	2349
Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Principal Investigator:	David H. Barlow, PhD
Department/School:	Psychology/CAS
Email:	dhbarlow@bu.edu
Telephone:	617-353-9610
Additional Contact Person:	Amantia Ametaj
Email:	amantiaa@bu.edu
Telephone:	617-353-9610

SECTION B: CHANGES MADE TO: (Check all that apply)

<input type="checkbox"/>	<u>Protocol Title</u> New Protocol Title:
<input checked="" type="checkbox"/>	<u>Consent/Assent Forms</u> Submit a tracked copy of the revised form
<input type="checkbox"/>	<u>Eligibility Criteria</u>

<input checked="" type="checkbox"/>	<u>Study Procedures</u>
<input type="checkbox"/>	<u>Total Number of Subjects</u> <ul style="list-style-type: none"> • Current Number Approved: • Requested New Number:
<input type="checkbox"/>	<u>Research Sites (Addition or Removal; provide a copy of the IRB approval letter for each site being added)</u> <ul style="list-style-type: none"> • Name of Site: • If IRB approval will not be obtained from the site, provide an explanation:
<input type="checkbox"/>	<u>Questionnaire/Survey (Revised/Addition/Removal)</u> Submit copies of any new or revised questionnaires/surveys. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Recruitment Methods or Materials</u> Submit copies of any new or revised recruitment materials. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Other</u> Provide a description of the change:

SECTION C: AMENDMENT DESCRIPTION

Provide a Brief Summary of the Change

We propose amending the waitlist period for participants who are randomized to this condition. Currently the waitlist period is 16 weeks from the date a participant is randomized to the condition. We would like to introduce more flexibility to the waitlist period by extending the period up to 21 weeks. This would allow longer windows for completing study assessments. Each participant would have the possibility of completing the waitlist in 16 weeks if he or she is able to complete study assessments in a timely manner. Also a waitlist period of up to 21 weeks would be more equitable with the time frame that the other two conditions are allotted.

Provide the Justification/Rationale for the Change

Will there be a change to the Risks or Benefits to the Subjects

SECTION D: RE-CONSENTING OF ALEADY ENROLLED SUBJECTS

If the requested change could affect a subject's willingness to continue taking part in the study, these subjects must be re-consented.

Could the requested change affect a subject's willingness to continue taking part in this research study?

YES*

NO

***If YES, please provide the plan for re-consenting already enrolled subjects**

SECTION E: PRINCIPAL INVESTIGATOR CERTIFICATION

The signature line below must be signed by the PI of the study. If the PI is a student then THIS form must also be signed by the Faculty Advisor.

By signing below I certify that:

- The information in this Application is true, complete, and accurate
- I will conduct this research in accordance with applicable laws, regulations, and BU CRC IRB policies

PI Printed Name: _____

PI Signature: _____ Date: _____

If PI is a student, signature of the faculty advisor is required below.
By signing, the faculty advisor is also indicating agreement with the statements above.

Faculty Advisor Printed Name: _____

Faculty Advisor Signature: _____ Date _____

Submission

This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

 N/A **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

 Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

David H. Barlow, PhD, Principal Investigator

Professor of Psychology and Psychiatry

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Amantia Ametaj, B.A., Research Assistant

Assistant to PI

(Address and phone same as PI)

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(Address and phone same as PI)

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C. Alex Brake

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. **Expected Duration of Study:** 5 years

7. **Description of Project.**

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

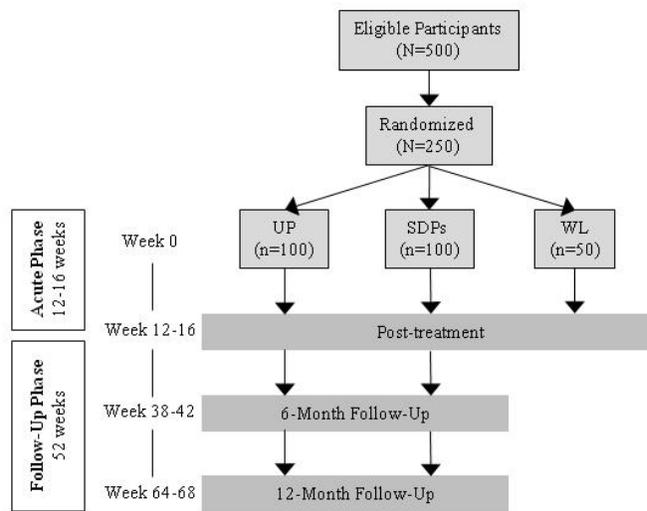
Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of

the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be

recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the

principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 to 21 weeks depending on how quickly they complete study assessments. These patients will be offered treatment at CARD free of charge following that 16 to 21 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report)

to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	6-Month and 12-Month Follow-Up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
MINI ADIS	* ²				
ADIS Super Lite	*		*	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	*		*	*	*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	*
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	*
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	*
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*	*	*	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*	*	*	*	*
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APQ; Rapee, Craske, & Barlow, 1994/1995)	*			*	*
Obsessive-Compulsive Inventory-Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	*			*	*
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	*			*	*
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	*
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		*	*	*
Eysenck Personality Questionnaire Revised-Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	*		*	*	*
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Symson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000)	* ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		

1. Collected to determine eligibility for research study.

2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline

3. Also collected at the end of session 2.

4. Collected at session 4 only

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994): ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCI; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation

(BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point

Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory

(WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for

supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-

pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to

answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinue psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or

active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is

likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

92. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
93. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
94. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
95. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
96. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
97. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
98. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging

inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.

- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



1/11/2013

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 14: Staff change



Amendment 15:

Boston University Charles River Campus Institutional Review Board

25 Buick Street

Room 157

Boston, Massachusetts 02215

T 617-358-6115 www.bu.edu/irb

Notification of IRB Review: Amendment

September 17, 2013

David Barlow, PhD Department of Psychology

648 Beacon Street

Boston, MA 02215

Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Protocol #:	2349
Funding Agency:	NIMH
Grant #:	NIMH
IRB Review Type:	1 R01 MH090053
IRB Review Action:	Full Board
	Requires Modification

Dear Professor Barlow:

On September 17, 2013, the IRB determined that the amendment request for the above-referenced study requires modifications in order to secure approval.

The modifications required are:

PROTOCOL

1. Please describe the procedure for waitlist subjects who elect to miss an assessment. For example, what would happen if a subject chooses to miss the 8-week assessment due to his or her own schedule constraints (e.g., vacation)? If a subject misses an assessment, what happens with the scheduling of subsequent assessments? Would the subject be permitted to continue participation in the study?

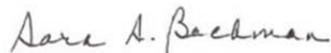
2. The amendment states that waitlist subjects who fail to respond to repeated contacts will be sent a letter and, should they fail to respond to the letter, will be withdrawn.
 - a. Please submit a copy of this withdrawal letter for IRB review.
 - b. Please describe what is meant by “repeated attempts.” How many attempts will be made prior to the letter and what is the timetable for these attempts at contact?
 - c. Please provide further information on the waitlist subjects’ care when withdrawn. That is, will subjects be followed for clinical care, will they be provided with a list of resources for treatment, or is there another plan in place for providing these withdrawn subjects with access to or references for treatment?

Please use the *Request for Modification Response* Form to respond to the modifications. The form can be located at <http://www.bu.edu/irb/>. In addition, please submit the following documents along with this form: 1) a copy of all revised documents in “Tracked Changes” format or similarly notated to indicate what changes were made and 2) a “clean” copy of all revised documents.

If a response to this letter is not received by the close of business on November 17, 2013 the IRB will withdraw the study from review.

If you have any questions, please contact Sonia Chawla Wright at 617-358-6115.

Sincerely,



Sara S. Bachman, PhD

Charles River Campus IRB Chair

NOTE: The changes requested in this amendment cannot be implemented until the modifications have been addressed and the IRB has approved the amendment

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

 N/A **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

 Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous

group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

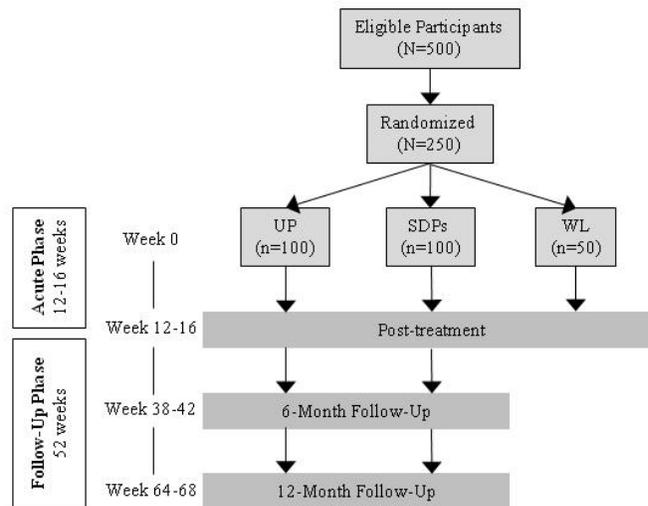
A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A),

Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of

the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years.

Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures,

Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks depending on how quickly they complete study assessments. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL

assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to

assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Assessment Measures	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12	Post-WL or Post-Tx	6-Month and 12-Month Follow-Up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	* ¹				
MINI ADIS	* ²				
ADIS Super Lite	*		*	*	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	*		*	*	*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*		*	*	*
Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Pirce, & Storch, 2006)	*		*	*	*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*		*	*	*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*		*	*	*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*		*	*	*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*		*	*	*
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*	*
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*	*	*	*	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*	*	*	*	*
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APQ; Rapee, Craske, & Barlow, 1994/1995)	*			*	*
Obsessive-Compulsive Inventory-Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	*			*	*
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	*			*	*
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		*	*	*
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		*	*	*
Eysenck Personality Questionnaire Revised-Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	*		*	*	*
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Symson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form MHC-SF (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000)	* ³				
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		* ⁴		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF; Tracey, T.J., & Kokotovic, A.M., 1989)			*		

1. Collected to determine eligibility for research study.

2. Administered only if 6 or more weeks lapse between ADIS-IV-L and baseline

3. Also collected at the end of session 2.

4. Collected at session 4 only

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994): ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and

scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is

sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the

beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCR; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation

(BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point

Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory

(WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilly & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for

supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-

pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to

answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinue psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or

active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that treatment sessions will occur at the CARD, but may involve completing exercises outside of the clinic which is consistent with good clinical practice at CARD. Further, patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some

deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

99. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item within the *Structured Interview Guide for the Hamilton Depression Rating Scale*. If, at any time, a participant indicates a score >1 on item 11, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
100. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
101. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
102. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
103. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them approximately every 4 weeks for assessment. All contact attempts to schedule assessments (for waitlist or immediate treatment participants) will be carefully documented in a retention tracking database by the Research Coordinator. The RC and project director will review this database on a weekly basis and address any reasons for non-compliance with completing assessments. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
104. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
105. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will periodically review any amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of

monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.

3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject’s medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



09/08/2013

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 16:

IRB Office use only Date submitted _____ Exp. Date _____ FB _____ Exp. _____

**BU Charles River IRB
Amendment Request Form**

This form is to be completed when a change (amendment) is requested to an IRB-approved study. **NOTE:** All changes must be approved by the IRB **PRIOR** to implementation.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study **WILL NOT CHANGE**. Previously approved versions of the consent forms should be archived as they are no longer valid and only the newly approved versions should be used.

Study Staff Changes: Changes to study staff can be made by submitting the Study Staff Amendment Form. This form is located on the IRB website at: <http://www.bu.edu/irb/>.

SECTION A: PROTOCOL AND CONTACT INFORMATION

Protocol Number:	2349
Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Principal Investigator:	David H. Barlow, Ph.D.
Department/School:	Psychology/CAS
Email:	dhbarlow@bu.edu
Telephone:	(617) 353-6338
Additional Contact Person:	Meghan Fortune
Email:	fortune@bu.edu
Telephone:	(617) 353-6338

SECTION B: CHANGES MADE TO: (Check all that apply)

NOTE: You must submit a clean and tracked copy of any documents (Application, consent form, letters, brochures, etc.) that are affected by the change

<input type="checkbox"/>	<u>Protocol Title</u> New Protocol Title:
<input type="checkbox"/>	<u>Consent/Assent Forms</u> Submit a tracked copy of the revised form

<input checked="" type="checkbox"/>	<u>Eligibility Criteria</u>
<input type="checkbox"/>	<u>Study Procedures</u>
<input type="checkbox"/>	<u>Total Number of Subjects</u> <ul style="list-style-type: none"> • Current Number Approved: • Requested New Number:
<input type="checkbox"/>	<u>Research Sites (Addition or Removal; provide a copy of the IRB approval letter for each site being added)</u> <ul style="list-style-type: none"> • Name of Site: • If IRB approval will not be obtained from the site, provide an explanation:
<input checked="" type="checkbox"/>	<u>Questionnaire/Survey (Revised/Addition/Removal)</u> Submit copies of any new or revised questionnaires/surveys. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Recruitment Methods or Materials</u> Submit copies of any new or revised recruitment materials. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Other</u> Provide a description of the change:

SECTION C: AMENDMENT DESCRIPTION

Provide a Brief Summary of the Change

- 1) We propose to add the Multidimensional Emotional Disorder Inventory (MEDI) to the self-report questionnaire battery. The MEDI will be administered at the following time points: baseline, session 4, session 8, session 12, post-treatment, 6 month follow-up, and 12 month follow-up. Although the addition of the MEDI is expected to increase the duration of the self-report questionnaires by 5 minutes on average, we do not expect any significant increase on participant burden or any additional risks.
- 2) We propose to recruit individuals who have been diagnosed with a principal anxiety disorder using criteria from either DSM-IV or DSM-5. The current application states that individuals may be eligible for the study if assigned a current, principal anxiety disorder by DSM-IV standards. However, we wish to extend the eligibility criterion to reflect current clinical standards and include DSM-5 anxiety disorders as well. In order to appropriately assign DSM-5 diagnoses, we wish to add the ADIS-5 to our clinician-rated assessment battery. Individuals will be assessed using either the ADIS-IV or ADIS-5 instrument throughout their participation in the research program depending on which version was completed at the time

of their baseline assessment. While there are some additional diagnoses in DSM-5, the overall length of the ADIS-5 is comparable to the length of an ADIS-IV assessment. Therefore, there is no expected additional burden on participants or any expected risks beyond already established potential risks of completing a diagnostic interview.

Provide the Justification/Rationale for the Change

- 1) The MEDI is a transdiagnostic measure that was created to target the underlying common features of internalizing disorders while capturing the phenotypic variances of anxiety and related disorders in their presentation. Therefore, the MEDI provides an opportunity to directly evaluate higher-order factors which have been identified in the development and maintenance of anxiety disorders within a transdiagnostic theoretical framework, and is consistent with the primary aims of the current study.
- 2) The proposed change is in response to the publication of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, and subsequent development of the ADIS-5. Additionally, the ADIS-5 has been implemented as the primary intake assessment to determine diagnoses at the Center for Anxiety and Related Disorders (CARD) which is the primary site of recruitment for the current research study. Therefore, by including the ADIS-5 to screen for (and include) DSM-5 diagnostic criteria, potential participants would have a greater chance of being enrolled in the study quicker without having to undergo further evaluation and undue burden (i.e. completing an ADIS-5 through CARD and then ADIS-IV at the baseline).

Will there be a change to the Risks or Benefits to the Subjects

- 1) We do not expect any additional risks beyond which have already been identified in completing self-report questionnaires relating to symptoms of anxiety and depression.
- 2) We do not expect any additional risks to participants beyond already identified risks of completing clinician-rated interviews which may cause some distress in confronting uncomfortable feelings.

SECTION D: RE-CONSENTING OF ALEADY ENROLLED SUBJECTS

If the requested change could affect a subject's willingness to continue taking part in the study, these subjects must be re-consented.

Could the requested change affect a subject's willingness to continue taking part in this research study?

YES*

NO

***If YES, please provide the plan for re-consenting already enrolled subjects**

SECTION E: PRINCIPAL INVESTIGATOR CERTIFICATION

The signature line below must be signed by the PI of the study. If the PI is a student then THIS form must also be signed by the Faculty Advisor.

By signing below I certify that:

- The information in this Application is true, complete, and accurate
- I will conduct this research in accordance with applicable laws, regulations, and BU CRC IRB policies

PI Printed Name: David H. Barlow

PI Signature:  Date: 01/15/2014

If PI is a student, signature of the faculty advisor is required below.

By signing, the faculty advisor is also indicating agreement with the statements above.

Faculty Advisor Printed Name: _____

Faculty Advisor Signature: _____ Date _____

Submission

This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

David H. Barlow, PhD, Principal Investigator

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617-232-9500

5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

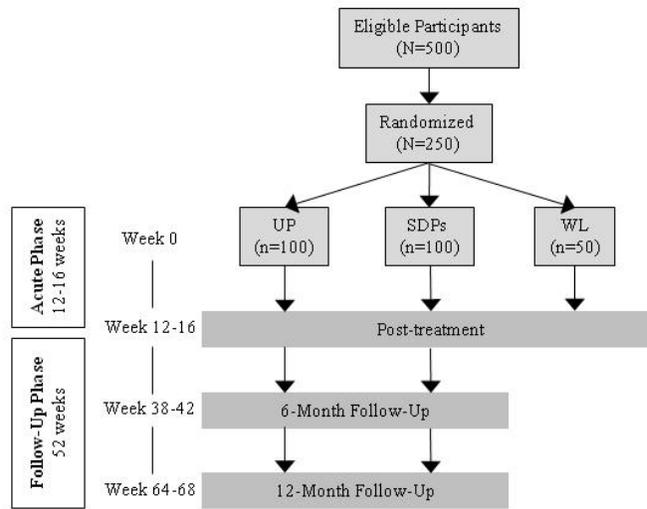
Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A

minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb

Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification.

Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures,

Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks depending on how quickly they complete study assessments. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation

in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to

assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12 & 16	Post-WL or Post-Tx	6-Month 12-Month Follow-
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	x ¹				
MINI ADIS	x ¹				
ADIS Super Lite	x		x	x	x
Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, in press)	x ¹				
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	x		x	x	x
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	x		x	x	x
Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989)	x		x	x	x
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	x		x	x	x
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	x		x	x	x
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	x		x	x	x
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	x		x	x	x
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	x		x	x	x
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	x	x	x	x	x
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	x	x	x	x	x
Multidimensional Emotional Disorder Inventory (MED; Rosellini, 2013)	x		x	x	x
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APPO; Rapee, Craske, & Barlow, 1994;1995)	x			x	x
Obsessive-Compulsive Inventory--Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	x			x	x
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	x			x	x
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow,	x		x	x	x

2004)					
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Behavioral Inhibition/ Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		*	*	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	*		*	*	*
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1988)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Simpson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAIS-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)		*2			
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		*3		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
1. Collected to determine eligibility for research study 2. Collected at the end of session 2 3. Collected at session 4 only					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994): ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, 2013): This semi-structured diagnostic clinical interview focuses on DSM-5 diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM-5 diagnostic criteria. Inquiries about suicidal ideation are part of this interview. In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-5 diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations

at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCI; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Multidimensional Emotional Disorders Inventory (MEDDI; Brown & Rosellini, 2012): The MEDDI is a 60-item questionnaire recently developed at our center as a measure of the dimensional classification system proposed by Brown and Barlow (2009) emphasizing common features of internalizing disorders but also encompassing the range of phenotypic expressions emanating from different foci of anxiety.

The MEDI assesses 10 dimensions, falling under 4 higher-order constructs: Temperament: neurotic temperament (NT), positive temperament (PT); Mood: depression/anhedonia (DEP); Focus of anxiety: somatic anxiety (SOM), panic/autonomic symptoms (PAS), intrusive cognitions (IC), social evaluation (SOC), past trauma (TRM); Avoidance: active avoidance (AV-A), passive avoidance (AV-P). Participants record responses on how they experience and respond to emotions. Responses are based on a 9-point Likert scale ranging from 0 (Not characteristic of me/does not apply to me) to 8 (Extremely characteristic of me/applies to me very much). Although dimensions in the MEDI are well established, there have been no prior attempts to develop and evaluate these constructs within a single assessment system. Unlike extant measures of various internalizing disorders that emphasize disorder-specific features, MEDI items were generated from a transdiagnostic perspective.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or

feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum

possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous

supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing

data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and p value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV or DSM-5 principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below) or Anxiety and Related Disorders Interview Schedule *DSM-5* (ADIS5; Brown & Barlow, 2013); and are rated as crossing the threshold for a formal *DSM-IV* or *DSM-5* diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinue psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that treatment sessions will occur at the CARD, but may involve completing exercises outside of the clinic which is consistent with good clinical practice at CARD. Further, patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

106.

Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item within the *Structured*

Interview Guide for the Hamilton Depression Rating Scale. If, at any time, a participant indicates a score >1 on item 11, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.

107. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
108. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
109. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
110. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them approximately every 4 weeks for assessment. All contact attempts to schedule assessments (for waitlist or immediate treatment participants) will be carefully documented in a retention tracking database by the Research Coordinator. The RC and project director will review this database on a weekly basis and address any reasons for non-compliance with completing assessments. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
111. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
112. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will periodically review any amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24

hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.

- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



01/15/2014

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 17: Staff changes

Amendment 18: Staff changes

Amendment 19: Staff Changes

Amendment 20:

IRB Office use only Date submitted _____ Exp. Date _____ FB _____ Exp. _____

**BU Charles River IRB
Amendment Request Form**

This form is to be completed when a change (amendment) is requested to an IRB-approved study. **NOTE:** All changes must be approved by the IRB **PRIOR** to implementation.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study **WILL NOT CHANGE**. Previously approved versions of the consent forms should be archived as they are no longer valid and only the newly approved versions should be used.

Study Staff Changes: Changes to study staff can be made by submitting the Study Staff Amendment Form. This form is located on the IRB website at:

<http://www.bu.edu/irb/application-forms/>.

SECTION A: PROTOCOL AND CONTACT INFORMATION

Protocol Number:	2349
Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Principal Investigator:	David H. Barlow, Ph.D.
Department/School:	Psychology/CAS
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Telephone:	(617)353-6338
Additional Contact Person:	Meghan Fortune
Email:	fortunem@bu.edu
Telephone:	(617)353-6338

SECTION B: CHANGES MADE TO: (Check all that apply)

NOTE: You must submit a clean and tracked copy of any documents (Application, consent form, letters, brochures, etc.) that are affected by the change

<input type="checkbox"/>	<u>Protocol Title</u> New Protocol Title:
<input checked="" type="checkbox"/>	<u>Consent/Assent Forms</u> Submit a tracked copy of the revised form

<input type="checkbox"/>	<u>Eligibility Criteria</u>
<input type="checkbox"/>	<u>Study Procedures</u>
<input type="checkbox"/>	<u>Total Number of Subjects</u> <ul style="list-style-type: none"> • Current Number Approved: • Requested New Number:
<input type="checkbox"/>	<u>Research Sites (Addition or Removal; provide a copy of the IRB approval letter for each site being added)</u> <ul style="list-style-type: none"> • Name of Site: • If IRB approval will not be obtained from the site, provide an explanation:
<input checked="" type="checkbox"/>	<u>Questionnaire/Survey (Revised/Addition/Removal)</u> Submit copies of any new or revised questionnaires/surveys. Revised documents should include tracking to indicate the location of the changes.
<input checked="" type="checkbox"/>	<u>Recruitment Methods or Materials</u> Submit copies of any new or revised recruitment materials. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Other</u> Provide a description of the change:

SECTION C: AMENDMENT DESCRIPTION

Provide a Brief Summary of the Change

1. First, we request to amend our current self-report questionnaire survey for the baseline and post (S16A) time points to include 4 additional questions from the PANAS-X to capture presence of anger symptoms.
2. Secondly, we request to amend our informed consent form by updating the confidentiality section to more accurately describe the location of where the treatment session audio recordings will be stored. We also would like to update the potential risks section by omitting the last paragraph to bring the informed consent form current with CARD clinic guidelines. Also, we would like to make minor adjustments throughout the informed consent form to correct awkward wording, as evidenced in the digital audio recordings signature section.
3. Lastly, we request permission to increase our recruitment efforts by posting information on the internet beyond our already approved study website by printing ads in local newspapers and establishing an online presence in community boards and social media forums related to anxiety and related mood disorders.

Provide the Justification/Rationale for the Change

1. The addition of these 4 items would provide necessary information for evaluating the relationship between anger, aggression, and anxiety symptoms.
2. We seek to make these changes to the informed consent form to improve the readability of the document and clearly communicate where the participants' information will be stored. We also want to clarify that while participants can come into CARD after completing their participation in the study for treatment, they will not necessarily automatically be granted 12 sessions free of charge. This last paragraph was in the current form on error, and we wish to correct it.
3. With the current lull in overall recruitment at CARD, we aim to bolster recruitment by disseminating information about the current treatment research options by posting in online community boards and on social media websites.

Will there be a change to the Risks or Benefits to the Subjects

1. We do not expect any change in risks or benefits to the subjects with the addition of these four items.
2. We do not expect any change in risks or benefits for the clarification to data storage procedures and other text updates. We also do not expect any change to potential risks or benefits since the CARD policy is not changing, but rather the text is being updated to accurately reflect the procedures. Participants will not be prevented from seeking care at CARD once they have completed the study; however they will be required to pay for their care.
3. We do not expect any change to the risks or benefits to the subjects.

SECTION D: RE-CONSENTING OF ALEADY ENROLLED SUBJECTS

If the requested change could affect a subject's willingness to continue taking part in the study, these subjects must be re-consented.

Could the requested change affect a subject's willingness to continue taking part in this research study?

YES*

NO

***If YES, please provide the plan for re-consenting already enrolled subjects**

SECTION E: PRINCIPAL INVESTIGATOR CERTIFICATION

The signature line below must be signed by the PI of the study. If the PI is a student then THIS form must also be signed by the Faculty Advisor.

By signing below I certify that:

- The information in this Application is true, complete, and accurate
- I will conduct this research in accordance with applicable laws, regulations, and BU CRC IRB policies

PI Printed Name: David H. Barlow

PI Signature:  Date: 6/9/2014

**If PI is a student, signature of the faculty advisor is required below.
By signing, the faculty advisor is also indicating agreement with the statements above.**

Faculty Advisor Printed Name: _____

Faculty Advisor Signature: _____ Date _____

Submission

This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous

group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

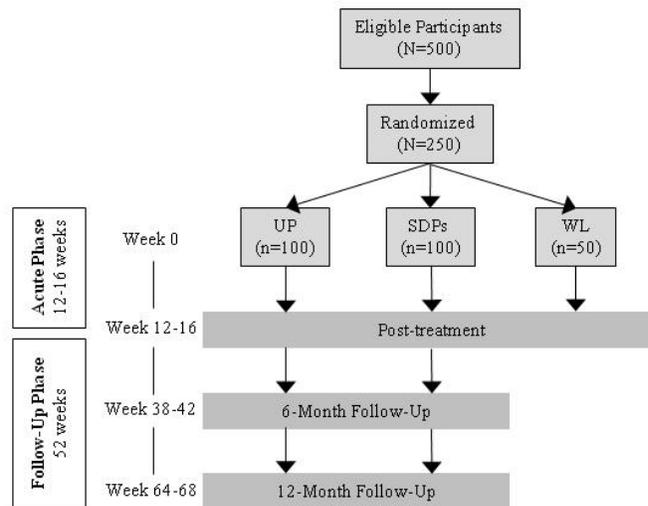
A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A),

Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of

the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



preliminary analyses, and the preparation of manuscripts.

Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures,

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years.

Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12 sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks depending on how quickly they complete study assessments. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL

assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to

assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12 & 16	Post-WL or Post-Tx	6-Month 12-Mon Follow-
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	✖ ¹				
MINI ADIS	✖ ¹				
ADIS Super Lite	✖		✖	✖	✖
Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, in press)	✖ ¹				
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	✖		✖	✖	✖
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	✖		✖	✖	✖
Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989)	✖		✖	✖	✖
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	✖		✖	✖	✖
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	✖		✖	✖	✖
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Behnap, Mazumdar, Houck, & Rollman, 2006)	✖		✖	✖	✖
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	✖		✖	✖	✖
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	✖		✖	✖	✖
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	✖	✖	✖	✖	✖
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	✖	✖	✖	✖	✖
Multidimensional Emotional Disorder Inventory (MED; Rosellini, 2013)	✖		✖	✖	✖
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994;1995)	✖			✖	✖
Obsessive-Compulsive Inventory--Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	✖			✖	✖
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	✖			✖	✖
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	✖		✖	✖	✖
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	✖		✖	✖	✖
Behavioral Inhibition/ Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	✖		✖	✖	✖
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	✖		✖	✖	✖

Emotion Regulation Questionnaire (ERO; Gross & John, 2003)	*		*	*	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	*		*	*	*
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1988)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Simpson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAIS-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)		*2			
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		*3		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
1. Collected to determine eligibility for research study 2. Collected at the end of session 2 3. Collected at session 4 only					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994): ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, 2013): This semi-structured diagnostic clinical interview focuses on DSM-5 diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM-5 diagnostic criteria. Inquiries about suicidal ideation are part of this interview. In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-5 diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations

at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCI; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Multidimensional Emotional Disorders Inventory (MEDDI; Brown & Rosellini, 2012): The MEDDI is a 60-item questionnaire recently developed at our center as a measure of the dimensional classification system proposed by Brown and Barlow (2009) emphasizing common features of internalizing disorders but also encompassing the range of phenotypic expressions emanating from different foci of anxiety.

The MEDI assesses 10 dimensions, falling under 4 higher-order constructs: Temperament: neurotic temperament (NT), positive temperament (PT); Mood: depression/anhedonia (DEP); Focus of anxiety: somatic anxiety (SOM), panic/autonomic symptoms (PAS), intrusive cognitions (IC), social evaluation (SOC), past trauma (TRM); Avoidance: active avoidance (AV-A), passive avoidance (AV-P). Participants record responses on how they experience and respond to emotions. Responses are based on a 9-point Likert scale ranging from 0 (Not characteristic of me/does not apply to me) to 8 (Extremely characteristic of me/applies to me very much). Although dimensions in the MEDI are well established, there have been no prior attempts to develop and evaluate these constructs within a single assessment system. Unlike extant measures of various internalizing disorders that emphasize disorder-specific features, MEDI items were generated from a transdiagnostic perspective.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or

feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum

possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous

supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing

data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and p value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV or DSM-5 principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below) or Anxiety and Related Disorders Interview Schedule *DSM-5* (ADIS5; Brown & Barlow, 2013); and are rated as crossing the threshold for a formal *DSM-IV* or *DSM-5* diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinue psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that treatment sessions will occur at the CARD, but may involve completing exercises outside of the clinic which is consistent with good clinical practice at CARD. Further, patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

113.

Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item within the *Structured*

Interview Guide for the Hamilton Depression Rating Scale. If, at any time, a participant indicates a score >1 on item 11, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.

114. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
115. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
116. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
117. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them approximately every 4 weeks for assessment. All contact attempts to schedule assessments (for waitlist or immediate treatment participants) will be carefully documented in a retention tracking database by the Research Coordinator. The RC and project director will review this database on a weekly basis and address any reasons for non-compliance with completing assessments. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
118. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
119. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will periodically review any amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24

hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.

- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



06/09/2014

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 21: Staff changes

Amendment 22:

IRB Office use only Date submitted _____ Exp. Date _____ FB _____ Exp. _____

**BU Charles River IRB
Amendment Request Form**

This form is to be completed when a change (amendment) is requested to an IRB-approved study.

NOTE: All changes must be approved by the IRB **PRIOR** to implementation.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study **WILL NOT CHANGE**. Previously approved versions of the consent forms should be archived as they are no longer valid and only the newly approved versions should be used.

Study Staff Changes: Changes to study staff can be made by submitting the Study Staff Amendment Form. This form is located on the IRB website at: <http://www.bu.edu/irb/application-forms/>.

SECTION A: PROTOCOL AND CONTACT INFORMATION

Protocol Number:	2349
Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Principal Investigator:	David H. Barlow, Ph.D.
Department/School:	Psychology/CAS
Email:	dhbarlow@bu.edu
Telephone:	(617)353-6338
Additional Contact Person:	Katherine Kennedy
Email:	kennedy7@bu.edu
Telephone:	(617)353-6338

SECTION B: CHANGES MADE TO: (Check all that apply)

NOTE: You must submit a clean and tracked copy of any documents (Application, consent form, letters, brochures, etc.) that are affected by the change

<input type="checkbox"/>	<u>Protocol Title</u> New Protocol Title:
<input type="checkbox"/>	<u>Consent/Assent Forms</u> Submit a tracked copy of the revised form

<input type="checkbox"/>	<u>Eligibility Criteria</u>
<input type="checkbox"/>	<u>Study Procedures</u>
<input type="checkbox"/>	<u>Total Number of Subjects</u> <ul style="list-style-type: none"> • Current Number Approved: • Requested New Number:
<input type="checkbox"/>	<u>Research Sites (Addition or Removal; provide a copy of the IRB approval letter for each site being added)</u> <ul style="list-style-type: none"> • Name of Site: • If IRB approval will not be obtained from the site, provide an explanation:
<input type="checkbox"/>	<u>Questionnaire/Survey (Revised/Addition/Removal)</u> Submit copies of any new or revised questionnaires/surveys. Revised documents should include tracking to indicate the location of the changes.
<input checked="" type="checkbox"/>	<u>Recruitment Methods or Materials</u> Submit copies of any new or revised recruitment materials. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Other</u> Provide a description of the change:

SECTION C: AMENDMENT DESCRIPTION

Provide a Brief Summary of the Change

We request permission to increase our recruitment efforts by posting information on the internet and in the community beyond our already approved study website by displaying posters and distributing postcards, printing ads in local newspapers, establishing an online presence in community boards and social media forums.

Provide the Justification/Rationale for the Change

With the current lull in overall recruitment at CARD, we aim to bolster recruitment by disseminating information about the current treatment research options by posting in online community boards, social media websites and in the community.

Will there be a change to the Risks or Benefits to the Subjects

We do not expect any change to the risks or benefits to the subjects.

SECTION D: RE-CONSENTING OF ALEADY ENROLLED SUBJECTS

If the requested change could affect a subject's willingness to continue taking part in the study, these subjects must be re-consented.

Could the requested change affect a subject's willingness to continue taking part in this research study?

YES*

NO

***If YES, please provide the plan for re-consenting already enrolled subjects**

SECTION E: PRINCIPAL INVESTIGATOR CERTIFICATION

The signature line below must be signed by the PI of the study. If the PI is a student then THIS form must also be signed by the Faculty Advisor.

By signing below I certify that:

- The information in this Application is true, complete, and accurate
- I will conduct this research in accordance with applicable laws, regulations, and BU CRC IRB policies

PI Printed Name: David H. Barlow

PI Signature:



Date: 7/24/2014

**If PI is a student, signature of the faculty advisor is required below.
By signing, the faculty advisor is also indicating agreement with the statements above.**

Faculty Advisor Printed Name: _____

Faculty Advisor Signature: _____ Date _____

Submission

This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.

Amendment 23:

IRB Office use only Date submitted _____ Exp. Date _____ FB _____ Exp. _____

BU Charles River IRB Amendment Request Form

This form is to be completed when a change (amendment) is requested to an IRB-approved study.

NOTE: All changes must be approved by the IRB **PRIOR** to implementation.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study **WILL NOT CHANGE**. Previously approved versions of the consent forms should be archived as they are no longer valid and only the newly approved versions should be used.

Study Staff Changes: Changes to study staff can be made by submitting the Study Staff Amendment Form. This form is located on the IRB website at: <http://www.bu.edu/irb/application-forms/>.

SECTION A: PROTOCOL AND CONTACT INFORMATION

Protocol Number:	2349
Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Principal Investigator:	David H. Barlow, Ph.D.
Department/School:	Psychology/CAS
Email:	dhbarlow@bu.edu
Telephone:	(617)353-6338
Additional Contact Person:	Katherine Kennedy
Email:	kennedy7@bu.edu
Telephone:	(617)353-6338

SECTION B: CHANGES MADE TO: (Check all that apply)

NOTE: You must submit a clean and tracked copy of any documents (Application, consent form, letters, brochures, etc.) that are affected by the change

<input type="checkbox"/>	<u>Protocol Title</u> New Protocol Title:
<input type="checkbox"/>	<u>Consent/Assent Forms</u> Submit a tracked copy of the revised form
<input type="checkbox"/>	<u>Eligibility Criteria</u>

<input type="checkbox"/>	<u>Study Procedures</u>
<input type="checkbox"/>	<u>Total Number of Subjects</u> <ul style="list-style-type: none"> • Current Number Approved: • Requested New Number:
<input type="checkbox"/>	<u>Research Sites (Addition or Removal; provide a copy of the IRB approval letter for each site being added)</u> <ul style="list-style-type: none"> • Name of Site: • If IRB approval will not be obtained from the site, provide an explanation:
<input type="checkbox"/>	<u>Questionnaire/Survey (Revised/Addition/Removal)</u> Submit copies of any new or revised questionnaires/surveys. Revised documents should include tracking to indicate the location of the changes.
<input checked="" type="checkbox"/>	<u>Recruitment Methods or Materials</u> Submit copies of any new or revised recruitment materials. Revised documents should include tracking to indicate the location of the changes.
<input checked="" type="checkbox"/>	<u>Other</u> Provide a description of the change: Edited phone screen and edited voicemail script

SECTION C: AMENDMENT DESCRIPTION

Provide a Brief Summary of the Change

Recruitment materials:

We request permission to increase our recruitment efforts by posting information on the internet and in the community beyond our already approved study website by displaying advertisements on social media forums. This approval would be in addition to all of our currently approved materials.

Phone screen and voicemail script:

We request permission to edit the content of our recruitment phone screen script and voicemail script by rearranging the order in which some already-approved information is presented, removing references to “the Center” in voicemail messages, and adding some additional questions regarding participants’ age, location, and referral source.

Provide the Justification/Rationale for the Change

Recruitment materials:

With the current lull in overall recruitment at CARD, we aim to bolster recruitment by disseminating information about the current treatment research options by posting in online community boards, social media websites and in the community.

Phone screen and voicemail script:

We aim to increase patient understanding by providing a clearer and more concise description of some study procedures and reorganizing the presentation of information about the different treatment protocols in a way that more clearly highlights the differences and similarities. We also aim to keep track of recruitment efforts and assess participants' initial eligibility at the start of our contact with them through the addition of questions regarding age, location, and referral source. Through the removal of references to the Center in the voicemail script, we aim to increase sensitivity to patient confidentiality.

Will there be a change to the Risks or Benefits to the Subjects

Recruitment materials, phone screen and voicemail script:

We do not expect any change to the risks or benefits to the subjects.

SECTION D: RE-CONSENTING OF ALEADY ENROLLED SUBJECTS

If the requested change could affect a subject's willingness to continue taking part in the study, these subjects must be re-consented.

Could the requested change affect a subject's willingness to continue taking part in this research study?

YES*

NO

***If YES, please provide the plan for re-consenting already enrolled subjects**

SECTION E: PRINCIPAL INVESTIGATOR CERTIFICATION

The signature line below must be signed by the PI of the study. If the PI is a student then THIS form must also be signed by the Faculty Advisor.

By signing below I certify that:

- The information in this Application is true, complete, and accurate
- I will conduct this research in accordance with applicable laws, regulations, and BU CRC IRB policies

PI Printed Name: David H. Barlow

PI Signature:  Date: 8/15/2014

If PI is a student, signature of the faculty advisor is required below.
By signing, the faculty advisor is also indicating agreement with the statements above.

Faculty Advisor Printed Name: _____

Faculty Advisor Signature: _____ Date _____

Submission

This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

__N/A__ **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

_____ **Expedited:** Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

David H. Barlow, PhD, Principal Investigator

Professor of Psychology and Psychiatry

Psychology Department

Boston University

Center for Anxiety and Related Disorders

648 Beacon St., 6th Floor

Boston, MA 02215

dhbarlow@bu.edu

617-353-9610

4. **Co-Investigators and Staff:**

Co-Investigators

Timothy A. Brown, PsyD, Co-Investigator, Biostatistician

Professor

Psychology Department

Boston University

Center for Anxiety and Related Disorders

tabrown@bu.edu

(Address and phone same as PI)

Todd J. Farchione, PhD, Co-Investigator, Project Director

Assistant Research Professor

Psychology Department

Boston University

Center for Anxiety and Related Disorders

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(Address and phone same as PI)

Staff

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Matthew Gallagher, Ph.D., Research Assistant

Assistant Research Professor

Psychology Department

Boston University

Center for Anxiety and Related Disorders

mwg@bu.edu

(Address and phone same as PI)

Nina Wong Sarver, Ph.D., Independent Evaluator (also listed below)

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

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NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes _____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients

with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

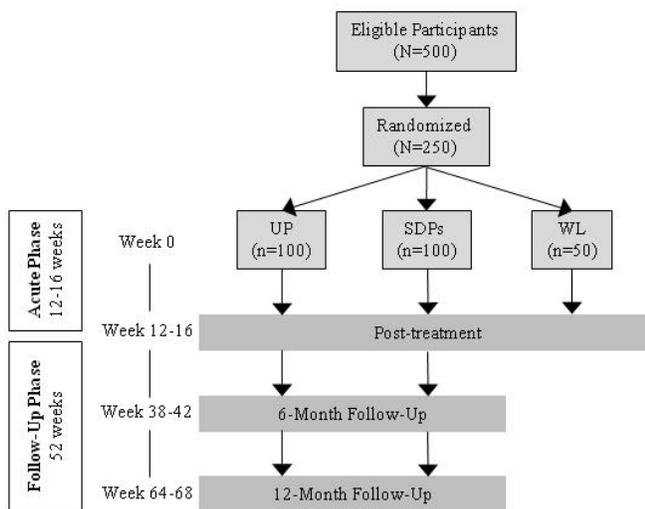
Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4

principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the

MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks depending on how quickly they complete study assessments. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12 & 16	Post-WL or Post-Tx	6-Month and 12-Month Follow-Up
Interview Based Assessments					
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	✕ ¹				
MINI ADIS	✕ ¹				
ADIS Super Lite	✕		✕	✕	✕
Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, in press)	✕ ¹				
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	✕		✕	✕	✕
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	✕		✕	✕	✕
Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989)	✕		✕	✕	✕
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	✕		✕	✕	✕
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	✕		✕	✕	✕
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	✕		✕	✕	✕
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	✕		✕	✕	✕
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	✕		✕	✕	✕
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	✕	✕	✕	✕	✕
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	✕	✕	✕	✕	✕
Multidimensional Emotional Disorder Inventory (MEDI; Rosellini, 2013)	✕		✕	✕	✕
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994;1995)	✕			✕	✕
Obsessive-Compulsive Inventory--Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	✕			✕	✕
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	✕			✕	✕
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	✕		✕	✕	✕

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		*	*	*
Behavioral Inhibition/ Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		*	*	*
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	*		*	*	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		*	*	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		*	*	*
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	*		*	*	*
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	*		*	*	*
Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1988)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Sympson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAIS-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)		*2			
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		*3		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
1. Collected to determine eligibility for research study 2. Collected at the end of session 2 3. Collected at session 4 only					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)); ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, 2013)): This semi-structured diagnostic clinical interview focuses on DSM-5 diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM-5 diagnostic criteria. Inquiries about suicidal ideation are part of this interview. In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-5 diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the

comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001):

The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that

patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman,

2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCR; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Multidimensional Emotional Disorders Inventory (MEDI; Brown & Rosellini, 2012): The MEDI is a 60-item questionnaire recently developed at our center as a measure of the dimensional classification system proposed by Brown and Barlow (2009) emphasizing common features of internalizing disorders but also encompassing the range of phenotypic expressions emanating from different foci of anxiety. The MEDI assesses 10 dimensions, falling under 4 higher-order constructs: Temperament: neurotic temperament (NT), positive temperament (PT); Mood: depression/anhedonia (DEP); Focus of anxiety: somatic anxiety (SOM), panic/autonomic symptoms (PAS), intrusive cognitions (IC), social evaluation (SOC), past trauma (TRM); Avoidance: active avoidance (AV-A), passive avoidance (AV-P). Participants record responses on how they experience and respond to emotions. Responses are based on a 9-point Likert scale ranging from 0 (Not characteristic of me/does not apply to me) to 8 (Extremely characteristic of me/applies to me very much). Although dimensions in the MEDI are well established, there have been no prior attempts to develop and evaluate these constructs within a single assessment system. Unlike extant measures of various internalizing disorders that emphasize disorder-specific features, MEDI items were generated from a transdiagnostic perspective.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, “Usually, when I have distressing thoughts or images” and continue with a mindfulness-related response, such as, “I am able just to notice them without reacting” and “I am able to accept the experience.” Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants’ “believability” in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual’s tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympton, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Deville & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will

be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to

determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV or DSM-5 principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below) or Anxiety and Related Disorders Interview Schedule *DSM-5* (ADIS5; Brown & Barlow, 2013); and are rated as crossing the threshold for a formal *DSM-IV* or *DSM-5* diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinuing psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that treatment sessions will occur at the CARD, but may involve completing exercises outside of the clinic which is consistent with good clinical practice at CARD. Further, patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged

to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

120. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item within the *Structured Interview Guide for the Hamilton Depression Rating Scale*. If, at any time, a participant indicates a score >1 on item 11, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
121. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
122. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.

123. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
124. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them approximately every 4 weeks for assessment. All contact attempts to schedule assessments (for waitlist or immediate treatment participants) will be carefully documented in a retention tracking database by the Research Coordinator. The RC and project director will review this database on a weekly basis and address any reasons for non-compliance with completing assessments. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
125. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
126. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will periodically review any amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting

clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.
4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.
- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



01/15/2014

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 24: Study Staff change

Amendment 25: Study Staff change

Amendment 26:

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. **Category of review (enter N/A if no claim is made):**

 N/A **Exempt:** Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

 Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. **Project Title:** Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. **Principal Investigator:**

David H. Barlow, PhD, Principal Investigator

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5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

Jane L. Pearson, Ph.D.

Division of Services and Intervention Research

NIMH, Rm 7139, MSC 9635

6001 Executive Blvd

Bethesda, MD 20892

Ph: 301-443-5898

Fax: 301-443-4045

Email: jp36u@nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No__X__

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

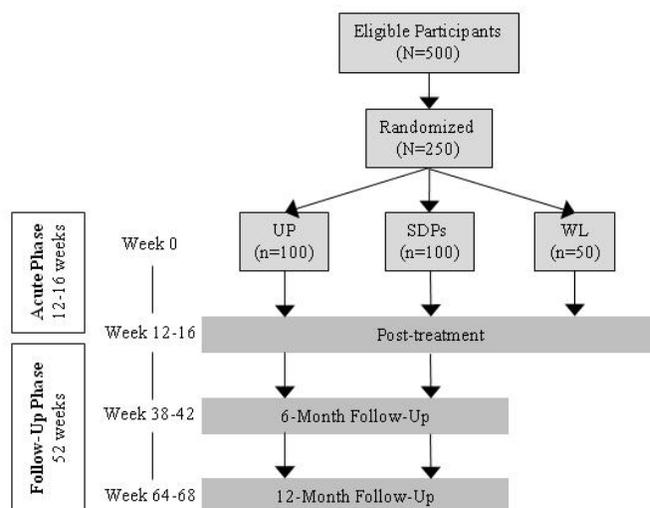
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last

approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks depending on how quickly they complete study assessments. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to five months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy).

Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule	TIME OF ADMINISTRATION				
	Baseline	Each Session	Sessions 4, 8, 12 & 16	Post-WL or Post-Tx	6-Month 12-Month Follow-

Interview Based Assessments

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	✖ ¹				
MINI ADIS	✖ ¹				
ADIS Super Lite	✖		✖	✖	✖
Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, in press)	✖ ¹				
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Bilt, & Rucci, 2001; Williams, 1988)	✖		✖	✖	✖
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	✖		✖	✖	✖
Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989)	✖		✖	✖	✖
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	✖		✖	✖	✖
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	✖		✖	✖	✖
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	✖		✖	✖	✖
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	✖		✖	✖	✖
Work and Social Adjustment Scale - Clinician Rated (WSAS; Marks, Connolly, & Hallam, 1973)	✖		✖	✖	✖
Diagnosis Non-specific Self-report Measures					
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	✖	✖	✖	✖	✖
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	✖	✖	✖	✖	✖
Multidimensional Emotional Disorder Inventory (MED; Rosellini, 2013)	✖		✖	✖	✖
Diagnosis Specific Self-report Measures					
Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994;1995)	✖			✖	✖
Obsessive-Compulsive Inventory--Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002)	✖			✖	✖
Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990)	✖			✖	✖
Potential Mediators of Treatment Change					
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	✖		✖	✖	✖
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	✖		✖	✖	✖
Behavioral Inhibition/ Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	✖		✖	✖	✖
Cognition Checklist-Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987)	✖		✖	✖	✖
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	✖		✖	✖	✖
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	✖		✖	✖	✖
Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011)	✖		✖	✖	✖
Emotion Awareness Subscale of Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)	✖		✖	✖	✖

Positive and Negative Affective Schedule - Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1988)	*		*	*	*
Savoring Beliefs Inventory (SBI; Bryant, 2003)	*			*	*
Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008)	*		*	*	*
Insomnia Severity Index (ISI; Morin, 1993)	*		*	*	*
Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)	*		*	*	*
State Hope Scale (SHS; Snyder, C.R., Simpson, S.C., Ybasco, F.C., Borders, T.F., Babyak, M.A., & Higgins, R.L., 1996)	*		*	*	*
Working Alliance Inventory-Short Form-Client Version (WAIS-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
Quality of Life and Well-being					
Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993)	*		*	*	*
Adult Mental Health Continuum-Short Form (MHC-SF; Keyes, 2005b, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009)	*		*	*	*
Potential Moderators of Treatment Outcome					
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)		*2			
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*		*3		
Other Measures					
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*			
Treatment Skills Usage Questionnaire					*
Working Alliance Inventory-Short Form-Therapist Version (WAI-SF, Tracey, T.J. & Kokotovic, A.M., 1989)			*		
1. Collected to determine eligibility for research study 2. Collected at the end of session 2 3. Collected at session 4 only					

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994): ADIS Superlite and Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994). These semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer a modified version of the ADIS designed for the purposes of assessing change in current symptomatology (*ADIS Super-Lite*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at our Center (Barlow et al. 2000). In cases where more than six weeks lapse between baseline and the initial CARD evaluation, patients will be administered a Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994) instead of the Super-Lite as part of the baseline assessment. All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, 2013): This semi-structured diagnostic clinical interview focuses on DSM-5 diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM-5 diagnostic criteria. Inquiries about suicidal ideation are part of this interview. In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift. Psychiatric disorders will be assessed with the ADIS-5 diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations

at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS;): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview-Second Edition (Y-BOCS-II; Goodman, Rasmussen, Price, & Storch, 2006): The Y-BOCS-II is a revised version of the Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman et al., 1989), an interview designed to assess the presence and severity of OCD symptoms. The Y-BOCS-II assesses insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 67-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 5 (extreme) scale, yielding obsession and compulsion subscale scores (0-25) and a total score (0-50). The Y-BOCS-II has demonstrated high internal consistency and inter-rater reliability as well as good convergent and discriminant validity (Storch et al., 2010). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degrees of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006). The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms. The measure will be given at the beginning of each treatment session as well as the baseline, session 4, session 8, session 12, session 16 as well as 6 and 12 month follow up assessments.

Albany Panic and Phobia Questionnaire (APPQ; Rapee, Craske, & Barlow, 1994/1995): The APPQ is a 27-item scale designed to measure fear in sensation-producing activities. The degree to which participants agree with each item is rated on a 9-point Likert-type scale, with higher scores indicating greater fear. The measure is comprised of three subscales, reflecting fear of agoraphobic situations (“Agoraphobia”), fear of activities that produce somatic sensations (“Interoceptive”), and fear of social situations (“Social Phobia”). In the present study, the 9-item Agoraphobia subscale and the 8-item Interoceptive subscale will be utilized as measures for panic disorder. Additionally, the 10-item Social Phobia subscale will be collected for social anxiety. The measure has exhibited strong psychometric support, including high levels of scale reliability and concurrent validity with lengthier measures (Brown, White, & Barlow, 2004).

Obsessive-Compulsive Inventory—Revised (OCI-R; Foa, Huppert, Leiberg, Langner, Kichic, Hajcak, & Salkovskis, 2002): The OCI-R is an 18-item measure designed to assess symptoms of obsessive-compulsive disorder. The revised 5-point Likert-scale measure improves upon the original Obsessive-Compulsive Inventory (OCI; Foa, Kozak, Salkovskis, Coles, & Amir, 1998) by eliminating redundancy and simplifying scoring to 6 subscales of washing, checking/doubting, obsessing, mental neutralizing, ordering, and hoarding. The measure has been shown to have both good reliability and convergent validity (Foa et al., 2002).

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): The PSWQ was developed as a measure of worry. The 16-item assessment consists of a 5-point Likert-type scale and reveals chronic, excessive and generalized criteria of worry relevant to generalized anxiety disorder. The measure has been shown to have strong internal consistency and good test-retest reliability (Meyer et al., 1990).

Multidimensional Emotional Disorders Inventory (MEDDI; Brown & Rosellini, 2012): The MEDDI is a 60-item questionnaire recently developed at our center as a measure of the dimensional classification system proposed by Brown and Barlow (2009) emphasizing common features of internalizing disorders but also encompassing the range of phenotypic expressions emanating from different foci of anxiety.

The MEDI assesses 10 dimensions, falling under 4 higher-order constructs: Temperament: neurotic temperament (NT), positive temperament (PT); Mood: depression/anhedonia (DEP); Focus of anxiety: somatic anxiety (SOM), panic/autonomic symptoms (PAS), intrusive cognitions (IC), social evaluation (SOC), past trauma (TRM); Avoidance: active avoidance (AV-A), passive avoidance (AV-P). Participants record responses on how they experience and respond to emotions. Responses are based on a 9-point Likert scale ranging from 0 (Not characteristic of me/does not apply to me) to 8 (Extremely characteristic of me/applies to me very much). Although dimensions in the MEDI are well established, there have been no prior attempts to develop and evaluate these constructs within a single assessment system. Unlike extant measures of various internalizing disorders that emphasize disorder-specific features, MEDI items were generated from a transdiagnostic perspective.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson, Clark, & Tellegen, 1994). The PANAS-X is a widely-used, reliable and valid self-report measure of affect (Watson & Clark, 1994). It includes several scales, assessing overall positive and negative affects as well as a number of specific affects. Each affect scale is comprised of a set of emotional adjectives (e.g., interested, upset, nervous); scales can be administered separately. Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or

feeling in general. The present study utilizes the scales for positive and negative affect, specific affects of sadness, joviality, self-assurance, fatigue, and serenity, and adds a few additional adjectives for important affects missing from the scales selected.

Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ is a 62-item scale designed to assess experiential avoidance, which is defined as the tendency to avoid negative internal experience (thoughts, emotions, physical sensations). The degree to which participants agree with each item is rated on a 6-point Likert-type scale, with higher scores indicating greater avoidance. The measure is comprised of six subscales: behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The measure has exhibited good internal consistency and a high degree of convergent and discriminant validity (Gamez et al., 2011).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 16-item self-report measure designed to assess two distinct emotion regulation strategies- cognitive reappraisal and emotion suppression. Participants use a 7-point Likert scale to rate their agreement with items. The reappraisal scale assesses the tendency to change the content of one's thoughts to improve mood; The suppression subscale assesses the degree to which responders conceal outward expression of their emotional experience. The ERQ has demonstrated good convergent and discriminant validity (Gross & John, 2003).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) includes six subscales assessing problems in adaptive emotion regulation which can be summed to form a total score. In the present study, only the 6-item (lack of) emotional awareness subscale will be collected. Respondents indicate the degree to which each statement applies to them on a 5-point Likert scale. The test-retest reliability of the DERS subscales was adequate (.68 for AWARENESS). The measure has high internal consistency, and adequate construct and predictive validity (Gratz & Roemer, 2004)

Southampton Mindfulness Questionnaire (SMQ; Chadwick et al., 2008) is a 16-item instrument assessing a mindful approach to distressing thoughts and images. All items begin with, "Usually, when I have distressing thoughts or images" and continue with a mindfulness-related response, such as, "I am able just to notice them without reacting" and "I am able to accept the experience." Items are rated on a 7-point Likert-type scale (strongly agree strongly disagree). The authors noted that items represent four aspects of mindfulness: mindful observation, letting go, nonaversion, and nonjudgment, but that a unidimensional factor structure provided the best fit to their data. Thus, the computation of subscale scores is not recommended. The authors reported good internal consistency ($\alpha = .89$), a significant correlation with the MAAS ($r = .57$), significant differences in the expected direction between meditators and nonmeditators, a significant positive correlation with mood ratings, and a significant increase in scores for participants in an MBSR course.

Cognition Checklist – Anxiety Subscale (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). The CCL-A is a reliable and valid self-report scale assessing frequency of typical maladaptive automatic thoughts that are associated with anxiety (Beck et al., 1987; Steer, Beck, Clark, & Beck, 1994). Participants record the frequency of 12 thoughts on a 5-point Likert scale (0=never to 4=always). In addition to the frequency scale, the present investigators have added a scale assessing participants' "believability" in each thought. Believability ratings are scored on the same 5-point scale.

Savoring Beliefs Inventory (SBI; Bryant, 2003). The SBI is a 24-item self-report questionnaire that assesses an individual's tendency to maintain versus dampen positive emotions. It is comprised of three subscales focused on measuring regulation of past, present, and future positive emotions. It has demonstrated high reliability as well as convergent and discriminant validity (Bryant, 2003).

Insomnia Severity Index (ISI; Morin, 1993). The ISI is a self-report inventory designed to assess current (within the past two weeks) symptoms of insomnia. This 7-item scale covers content corresponding in part to DSM-IV criteria for insomnia, and measures perceived severity of insomnia symptoms, distress, and daytime impairment. The ISI shows good internal consistency and test-retest reliability (Bastien, Vallieres, & Morin, 2001; Blais et al., 1997).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a self-report inventory designed to measure retrospective sleep quality and disturbances over a 1-month interval. The PSQI assesses a broad range of domains, including sleep latency, duration of sleep, frequency and severity of specific sleep-related problems, and daytime function. The PSQI has excellent psychometric properties, and is commonly used in assessment and treatment studies of insomnia.

State Hope Scale (SHS; Snyder, Sympson, Ybasco, Borders, Babyak, & Higgins, R. L. 1996). The SHS is a 6-item self-report measure designed to assess hope and the importance of positive expectations for the future in promoting mental health and resilience. The measure has shown internal consistency and convergent and discriminant validity (Snyder et al., 1996).

Adult Mental Health Continuum-Short Form (MHC-SF; (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009). The MHC-SF is a 14-item self-report measure with a scale ranging from 0 (Never) to 5 (Every day). The measure is designed to assess social, emotional and psychological well-being. The measure has shown excellent internal consistency and discriminant validity in both adolescents and adults in the U.S., the Netherlands, and in South Africa (Keyes, 2005, 2006; Keyes et al., 2008; Lamers et al., 2011; Westerhof & Keyes, 2009).

Working Alliance Inventory – Short Form Client Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency ($\alpha = 0.98$) and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clients 2-3 minutes to complete.

Measures of Functional Impairment and Quality of Life

Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee, Harrison, & Blumenthal, 1993). The Q-LES-Q is a self-report measure that assesses the degree of satisfaction and enjoyment experienced over the past week. The measure consists of 14 items and assesses satisfaction across the following domains: physical health; mood; work; household activities; social relationships; family relationships; leisure activities; daily functioning; sexual drive and interest; economic status; living situation; physical stability; vision; and overall sense of well-being. Each item is rated on a Likert scale from 1-5 (Very Poor to Very Good). An individual's score is calculated as a percentage of the maximum

possible score (70), where a higher score indicates a better perceived quality of life. The Q-LES-Q has demonstrated high internal consistency and good construct validity (Ritsner et al., 2002)

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of Study Integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Working Alliance Inventory – Short Form Therapist Self-Report Version (WAI-SF-SR; Tracey, & Kokotovic, 1989). The WAI-SF-SR is a 12-item measure derived from the 36-item Working Alliance Inventory (WAI; Horvath & Greenberg, 1989), which is the most extensively used measure of the working alliance in mental health research. The 12-item version has excellent overall internal consistency and there is strong evidence for concurrent and predictive validity (Tracey & Kokotovic, 1989). This brief version uses a Likert scale with response options 1-7, and typically takes clinicians 2-3 minutes to complete.

Measures of Post-Treatment Skills Utilization

Treatment Skills Usage Questionnaire: a 10 item questionnaire, mainly comprised of yes or no answers with one Likert scale 1-7 response option, which assesses the utilization and practice of skills learned during treatment in the post-treatment time period.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O’Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). In an effort to control for therapist effects, Therapists will be certified and trained in both the UP and SDPs and will administer treatment in both approaches (UP and SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous

supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve an overall adherence rating of 80% or higher and/or a competence rating of "at least adequate," as indicated by receiving a 3 or higher on a scale ranging from 0-5, where the scale rates how effectively therapists delivered the key components of treatment. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing

data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and p value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited among individuals presenting for treatment at CARD and from the community using internet and paper advertising. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive active treatment following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV or DSM-5 principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below) or Anxiety and Related Disorders Interview Schedule *DSM-5* (ADIS5; Brown & Barlow, 2013); and are rated as crossing the threshold for a formal *DSM-IV* or *DSM-5* diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. The exception to this criterion will be marijuana, caffeine and/or nicotine abuse and nicotine and/or caffeine dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years. In addition, patients will be asked to refrain from seeking or discontinue psychotherapy outside of the study for their anxiety or mood symptoms for the duration of the waitlist or active treatment period. If the patient is unwilling to refrain or discontinue outside psychotherapy prior to entering the study they will be excluded from entering the trial.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that treatment sessions will occur at the CARD, but may involve completing exercises outside of the clinic which is consistent with good clinical practice at CARD. Further, patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

127.

Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item within the *Structured*

Interview Guide for the Hamilton Depression Rating Scale. If, at any time, a participant indicates a score >1 on item 11, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.

128. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
129. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
130. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
131. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them approximately every 4 weeks for assessment. All contact attempts to schedule assessments (for waitlist or immediate treatment participants) will be carefully documented in a retention tracking database by the Research Coordinator. The RC and project director will review this database on a weekly basis and address any reasons for non-compliance with completing assessments. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
132. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
133. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will periodically review any amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24

hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.

- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.



011/12/2014

Signature of Principal Investigator

Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department

Date

Amendment 27: Study Staff change

Amendment 28:

IRB Office use only Date submitted _____ Exp. Date _____ FB _____ Exp. ____

**BU Charles River IRB
Amendment Request Form**

This form is to be completed when a change (amendment) is requested to an IRB-approved study. **NOTE:** All changes must be approved by the IRB **PRIOR** to implementation.

If the changes in this amendment require modification to the informed consent, a new version of the informed consent will be approved and validated with an approval date. The expiration date of the study **WILL NOT CHANGE**. Previously approved versions of the consent forms should be archived as they are no longer valid and only the newly approved versions should be used.

Study Staff Changes: Changes to study staff can be made by submitting the Study Staff Amendment Form. This form is located on the IRB website at:

<http://www.bu.edu/irb/application-forms/>.

SECTION A: PROTOCOL AND CONTACT INFORMATION

Protocol Number:	2349
Protocol Title:	Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders
Principal Investigator:	David H. Barlow, Ph.D.
Department/School:	Psychology/CAS
Email:	dhbarlow@bu.edu
Telephone:	(617)353-6338
Additional Contact Person:	Katherine Kennedy
Email:	Kennedy7@bu.edu
Telephone:	(617)353-6338

SECTION B: CHANGES MADE TO: (Check all that apply)

NOTE: You must submit a clean and tracked copy of any documents (Application, consent form, letters, brochures, etc.) that are affected by the change

<input type="checkbox"/>	<u>Protocol Title</u> New Protocol Title:
<input type="checkbox"/>	<u>Consent/Assent Forms</u> Submit a tracked copy of the revised form

<input type="checkbox"/>	<u>Eligibility Criteria</u>
<input type="checkbox"/>	<u>Study Procedures</u>
<input type="checkbox"/>	<u>Total Number of Subjects</u> <ul style="list-style-type: none"> • Current Number Approved: • Requested New Number:
<input type="checkbox"/>	<u>Research Sites (Addition or Removal; provide a copy of the IRB approval letter for each site being added)</u> <ul style="list-style-type: none"> • Name of Site: • If IRB approval will not be obtained from the site, provide an explanation:
<input type="checkbox"/>	<u>Questionnaire/Survey (Revised/Addition/Removal)</u> Submit copies of any new or revised questionnaires/surveys. Revised documents should include tracking to indicate the location of the changes.
<input checked="" type="checkbox"/>	<u>Recruitment Methods or Materials</u> Submit copies of any new or revised recruitment materials. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Other</u> Provide a description of the change:

SECTION C: AMENDMENT DESCRIPTION

Provide a Brief Summary of the Change

We would like to change our study recruitment website to reflect that we have completed recruitment.

Our website can be found at: <http://bostonanxietytreatment.com/>. We wish to change the “Home”, “Join Our Study”, and “Contact Us” pages.

On the “Home” page, we wish to change, “You may be eligible to receive treatment at no cost in our Anxiety Disorders Treatment Study.” to: “Please contact us at: 617-353-9610”

On the “Join Our Study” page, we wish to remove all current text and replace with, “At the present time we are no longer recruiting individuals for any studies. Please check back periodically for new research opportunities.”

On the “Contact Us” page, we wish to remove “Please email our study staff at

bostonanxiety.bu@gmail.com or call at 857-998-3255 for more details on the Anxiety Disorders Treatment Study. They will be happy to speak with you about our treatment study and answer any questions you may have. (Also, please see our map for exact location below)”.

Provide the Justification/Rationale for the Change

We would like to maintain an up to date study website to provide current information to potential study participants.

Will there be a change to the Risks or Benefits to the Subjects

We do not anticipate a change to the risks or benefits to the subjects.

SECTION D: RE-CONSENTING OF ALEADY ENROLLED SUBJECTS

If the requested change could affect a subject’s willingness to continue taking part in the study, these subjects must be re-consented.

Could the requested change affect a subject’s willingness to continue taking part in this research study?

YES*

NO

***If YES, please provide the plan for re-consenting already enrolled subjects**

SECTION E: PRINCIPAL INVESTIGATOR CERTIFICATION

The signature line below must be signed by the PI of the study. If the PI is a student then THIS form must also be signed by the Faculty Advisor.

By signing below I certify that:

- The information in this Application is true, complete, and accurate
- I will conduct this research in accordance with applicable laws, regulations, and BU CRC IRB policies

PI Printed Name: _____David H. Barlow_____



PI Signature: _____

Date: _____3/19/2015_____

If PI is a student, signature of the faculty advisor is required below.

By signing, the faculty advisor is also indicating agreement with the statements above.

Faculty Advisor Printed Name: _____

Faculty Advisor Signature: _____ Date _____

Submission

This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.

Amendment 29:

IRB Office use only Date submitted _____ Exp. Date _____ FB _____ Exp. ____

**BU Charles River IRB
Amendment Request Form**

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Department/School:	Psychology/CAS
Email:	dhbarlow@bu.edu
Telephone:	(617)353-6338
Additional Contact Person:	Katherine Kennedy
Email:	Kennedy7@bu.edu
Telephone:	(617)353-6338

SECTION B: CHANGES MADE TO: (Check all that apply)

NOTE: You must submit a clean and tracked copy of any documents (Application, consent form, letters, brochures, etc.) that are affected by the change

<input type="checkbox"/>	<u>Protocol Title</u> New Protocol Title:
<input type="checkbox"/>	<u>Consent/Assent Forms</u> Submit a tracked copy of the revised form

<input type="checkbox"/>	<u>Eligibility Criteria</u>
<input checked="" type="checkbox"/>	<u>Study Procedures</u>
<input type="checkbox"/>	<u>Total Number of Subjects</u> <ul style="list-style-type: none"> • Current Number Approved: • Requested New Number:
<input type="checkbox"/>	<u>Research Sites (Addition or Removal; provide a copy of the IRB approval letter for each site being added)</u> <ul style="list-style-type: none"> • Name of Site: • If IRB approval will not be obtained from the site, provide an explanation:
<input type="checkbox"/>	<u>Questionnaire/Survey (Revised/Addition/Removal)</u> Submit copies of any new or revised questionnaires/surveys. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Recruitment Methods or Materials</u> Submit copies of any new or revised recruitment materials. Revised documents should include tracking to indicate the location of the changes.
<input type="checkbox"/>	<u>Other</u> Provide a description of the change:

SECTION C: AMENDMENT DESCRIPTION

Provide a Brief Summary of the Change

DSMB meetings will be completed in early fall instead of late spring.

Provide the Justification/Rationale for the Change

The 2015 meeting will occur after all participants have finished the acute phase of the trial so that the DSMB can review all treatment data, all future DSMB meetings going forward will occur in the fall. This decision was discussed with the IRB, DSMB chair, and the NIH project officer, who all agreed that conducting the meeting in the fall would be appropriate and would provide the clearest indication of how subjects are doing.

Will there be a change to the Risks or Benefits to the Subjects

We do not anticipate a change to the risks or benefits to the subjects.

SECTION D: RE-CONSENTING OF ALEADY ENROLLED SUBJECTS

If the requested change could affect a subject's willingness to continue taking part in the study, these subjects must be re-consented.

Could the requested change affect a subject's willingness to continue taking part in this research study?

YES*

NO

***If YES, please provide the plan for re-consenting already enrolled subjects**

SECTION E: PRINCIPAL INVESTIGATOR CERTIFICATION

The signature line below must be signed by the PI of the study. If the PI is a student then THIS form must also be signed by the Faculty Advisor.

By signing below I certify that:

- The information in this Application is true, complete, and accurate
- I will conduct this research in accordance with applicable laws, regulations, and BU CRC IRB policies

PI Printed Name: _____ David H. Barlow

PI Signature: _____  _____ Date: ___ 6.25.2015 ___

If PI is a student, signature of the faculty advisor is required below.
By signing, the faculty advisor is also indicating agreement with the statements above.

Faculty Advisor Printed Name: _____

Faculty Advisor Signature: _____ Date _____

Submission

This form can be completed, signed, scanned and submitted to the IRB at irb@bu.edu. Faxed documents and handwritten materials are not accepted. Be sure to include all relevant attachments.

Amendment 30:

Application No. _____

Date Received _____

IRB RESEARCH APPLICATION

Two copies of the completed, typewritten, and signed research application should be submitted to the Institutional Review Board, 25 Buick St., Boston, MA, 02215, with two copies of the full grant proposal (including appendices but excluding budgets). Any documents pertaining to the review of the research by another IRB should also be included. Two copies of an informed consent form, and assent form if applicable, must accompany the application.

Questions concerning this application or the application process should be directed to the Coordinator for the Board at (617) 358-6115.

1. Category of review (enter N/A if no claim is made):

N/A Exempt: Applicants may claim exemption from further review if the research is in accordance with Appendix A (see attached); applicants must cite the applicable regulation.

Expedited: Applicants requesting expedited review must cite the applicable regulation in Appendix B (see attached).

2. Project Title: Efficacy Evaluation of a Unified Transdiagnostic Treatment for Anxiety Disorders

3. Principal Investigator:

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Doctoral Candidate in Clinical Psychology at Boston University

(Address and phone same as PI)

3 Post-Doctoral Research Associates

Personnel for these positions are *to be determined*. IRB amendments with detailed personnel information for these positions will be submitted as soon as personnel are identified.

4 Graduate Research Assistants

Personnel for these positions are *to be determined*. IRB amendments with detailed personnel information for these positions will be submitted as soon as personnel are identified.

1 Research Technician

The individual for this position is *to be determined*. An IRB amendment with detailed information for this position will be submitted as soon as personnel is identified.

Data and Safety Monitoring Board (DSMB)

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- 5. Granting Agency and Date of Submission (include name, address, phone number, and fax number of program officer as well as the sponsor grant number and Boston University Restricted Fund Account number if available--enter N/A if appropriate):**

Granting Agency: National Institute of Mental Health

Date of Submission: March 2010

Program Officer:

David I. Sommers, Ph.D., ABPP

Scientific Review Officer

National Institute of Mental Health

6001 Executive Boulevard

Room 6144, MSC 9606

Bethesda, MD 20892

voice - 301-443-7861

fax - 301-443-4720

email - dsommers@mail.nih.gov

NIMH Grant Number: 1 R01 MH090053

Boston University Restricted Fund Account number: To be assigned.

Note: Please attach PI and Co-I Conflict of Interest Disclosure forms if the study is not externally funded. For grant-related studies, please indicate whether an investigator conflict of interest has been disclosed to the CRC Office of Sponsored Programs. Yes_____ No X

6. Expected Duration of Study: 5 years

7. Description of Project.

A.1. Objectives and expected outcomes

The purpose of this proposal is to evaluate efficacy of the recently developed Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). This protocol takes advantage of recent advances in our understanding of the nature of anxiety disorders, as well as emerging knowledge of the process of regulation and change in anxious behavior, in order to distill and refine basic principles of successful psychological treatments for anxiety disorders. It is expected that this approach will simplify training and dissemination, provide better coverage for comorbid conditions, cover “not otherwise specified” (NOS) and sub-definitional threshold presentations, possibly improve efficacy particularly in the long term, and perhaps also shed further light on the nature of anxiety disorders. Thus, the major aims of this proposal are to:

Primary Aims

Aim 1: Evaluate the efficacy of the UP applied to a group of patients with heterogeneous anxiety disorders as compared to a group receiving existing evidence-based single diagnosis treatment protocols (SDPs) benchmarked against a wait list control condition (WL) to determine the treatment responsiveness of the sample on common measures of outcome.

Hypothesis 1: Using equivalence analysis, we hypothesize that UP will be statistically equivalent to SDPs in acute symptom reduction from pre- to post-treatment when applied across a heterogeneous group of patients with anxiety disorders. Statistical equivalence indicates that there is no clinically meaningful difference between the two treatments using criteria specified *a priori*.

Aim 2: Evaluate the efficacy of both the UP and SDPs relative to a benchmark WL condition.

Hypothesis 2a: We hypothesize that UP will be superior to WL in acute symptom reduction from pre- to post-treatment.

Hypothesis 2b: We hypothesize that SDPs will be superior to WL in acute symptom reduction from pre- to post-treatment.

Aim 3: Determine long-term efficacy of UP relative to SDPs over a 1-year period following treatment discontinuation.

Hypothesis 3a: We hypothesize that UP will result in continued treatment gains over the 6- and 12-month follow-up period following treatment discontinuation.

Hypothesis 3b: We hypothesize that UP will produce significantly better functioning at a 1-year follow-up compared to SDPs.

Aim 4: Examine the relative effects of each active treatment approach (UP & SDPs) on comorbid anxiety and depressive disorder severity.

Hypothesis 4a: We hypothesize that UP will result in greater reductions in comorbid disorder severity at both acute and follow-up assessments compared to SDPs.

Secondary Aims

Aim 5: Ascertain the relative effects of each active treatment on higher-order temperamental indices.

Hypothesis 5: Although all active treatments will result in a significant pre- to post-treatment reduction in neuroticism, we hypothesize that this reduction will be significantly larger in UP condition relative to SDPs.

Aim 6: Determine if change in higher order temperamental variables mediates long term outcome.

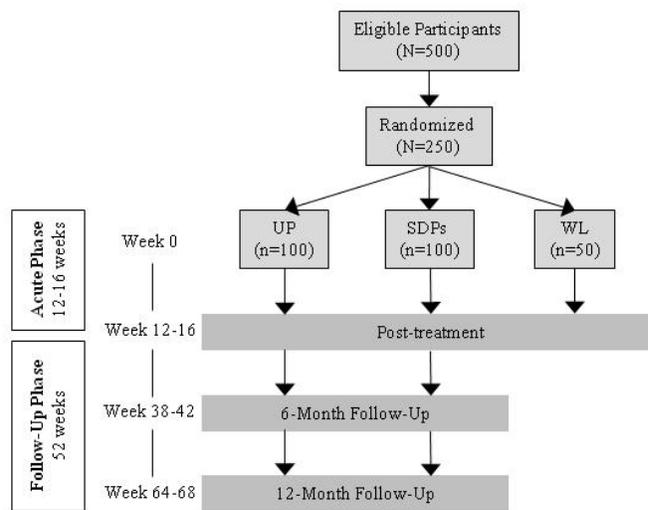
Hypothesis 6: We hypothesize that the differential efficacy of treatment on long-term outcome will be mediated by changes in neuroticism during the acute treatment phase.

Exploratory analyses will examine additional mediators and moderators of treatment response at both acute, 6-month, and 12-month follow-up.

A.2. Experimental Design

A heterogeneous sample of 250 patients meeting diagnostic criteria for at least one of four anxiety disorders: Social Phobia (SAD), Panic Disorder with or without Agoraphobia (PD/A), Generalized Anxiety Disorder (GAD), or Obsessive Compulsive Disorder (OCD) (see below) will be randomized to one of three treatment cells (see Figure 1 below): (1) UP; (2) SDPs; or (3) WL. A minimum of 50 patients from each of the 4 principal diagnostic categories will be included in the randomization to ensure adequate representation of each anxiety disorder, a strategy recommended to sustain or increase power (cf. Kraemer & Fendt, 1990). The study will consist of two phases: (1) a 12 or 16 week acute treatment phase (or 16 week WL) and (2) a 12-month follow-up phase, during which active treatments will be discontinued and patients will be followed to assess the long-term effects of treatment (outcome measures are discussed below). WL participants will not be included in the follow-up phase of the study. Rather, they will immediately receive treatment at the end of the sixteen week waiting period.

Figure 1. Study Flow Diagram



Timetable. The duration of this study will be 5 years. The first 9 months of the project will be dedicated to hiring staff and therapist training and certification. Recruitment will begin in the 9th month of Year 1. Approximately 5-8 new participants will be recruited per month, with a total of 20 participants in Year 1, 66 participants in Year 2, 84 participants in Year 3, and 80 participants in Year 4. Year 4 will see the completion of the treatment phase. Year 5 will be devoted to follow-up assessments, the completion of data entry and data management procedures, preliminary analyses, and the preparation of manuscripts.

Setting. All treatments will be conducted at the CARD, which is one of the largest research clinics devoted to anxiety and related emotional disorders in the world and maintains a substantial patient flow. The clinic consists of approximately 15,000 sq. ft. of space and includes multiple individual and group treatment rooms and full-time administrative staff including two receptionists covering the front desk during the 12-hour clinic day (8 a.m. through 8 p.m.). Staff members include licensed psychologists, a psychiatrist, a nurse, research technicians, doctoral students from clinical psychology and counseling psychology, and psychiatric residents.

Treatment Conditions and Specifications

Single diagnosis treatment protocols (SDPs). Four disorder-specific cognitive-behavioral treatments will be conducted in accordance with treatment manuals of demonstrated efficacy. SDPs will

be matched to the principal anxiety disorder diagnosis. In the rare case of coprincipal diagnoses, patients will be given the choice of which diagnosis they would like to focus on in treatment, as is customary in real world applications of SDPs. Individual treatment sessions will be conducted by experienced clinicians who will be certified in the administration of these protocols (see certification procedures described below). A workbook will be provided to each patient as part of these manualized treatments. These 4 SDPs were chosen because they are widely used with substantive evidence for efficacy. Furthermore, we are intimately familiar with these protocols having used them daily for over 20 years. Two of them were developed by the PI and Dr. Michelle Craske and their associates, and a third was developed at our Center when it was in Albany by Dr. Rick Heimberg and associates including Dr. Deb Hope. All SDPs are published and available in the “Treatments That Work” series of which the PI is Editor-in-Chief. The treatment protocols are as follows: Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach (MSA; Hope, Heimberg, Juster, & Turk, 2000, Hope, Heimberg, & Turk, 2006); Mastery of Anxiety and Panic - IV (MAP-IV; Barlow and Craske, 2000, 2007); Mastery of Anxiety and Worry - II (MAW-II; Zinbarg, Craske, & Barlow, 1994, 2006); and Obsessive-Compulsive Disorder: A Cognitive Behavioral Therapy Approach (Kozak & Foa, 1997, Foa & Kozak, 2004; Foa, Yadin, & Lichner, 2008). As recommended by the treatment developers, the MSA, MAW, and OCD protocols will be conducted over the course of 16 sessions, while the MAP-IV will be conducted over 12-sessions. All treatments will be administered in an individual format and treatment sessions will last approximately 50-60 minutes, with the exception of the OCD protocol, which may continue for up to 90 minutes.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP). The UP will be individually administered in accordance with a treatment protocol. As previously described, this protocol is designed to help patients learn how to confront and experience uncomfortable emotions and learn how to respond to their emotions in more adaptive ways. Individual treatment sessions will be conducted by experienced clinicians who will be trained in the administration of this protocol. A workbook will be provided to each patient as part of this manualized treatment. Treatment and session length of the UP will be matched to the SDPs for each principal diagnosis (see description above). Thus, treatment will consist of 12 or 16 weekly sessions, depending on principal diagnosis. In cases where the principal diagnosis is GAD, SAD, or PD/A sessions will last 50-60 minutes. For principal diagnosis of OCD, treatment sessions may last up to 90 minutes. While the modularized design of the UP offers greater flexibility in the administration of key treatment elements, for the purposes of this study, all modules will be administered in a set order to ensure that the sequencing of treatment components is the same across patients, although length of modules may vary. The efficacy of the UP has been previously tested in 2 open clinical trials, as well as in a recently completed randomized clinical trial. The results of the two open clinical trials have been published (see Ellard et al., 2010), and show up to 73% of patients reaching responder status after treatment.

Waitlist control. Patients in the waitlist condition will not receive any active treatment for a period of 16 weeks. These patients will be offered treatment at CARD free of charge following that 16 week period, which will not be an undue burden as patients typically wait two to four months for treatment at our Center. Patients in the waitlist condition will be asked to complete three brief assessments of current symptoms during the waitlist period (at approximately 4, 8, and 12 weeks). Any patient showing significant deterioration during the waitlist period will be removed from the study and given appropriate treatment or referred to another provider.

Post-Treatment Period. At the conclusion of the treatment, patients receiving psychological treatments will be encouraged to continue applying the strategies learned in treatment. Continued practice of the interventions is considered part of treatment, and patients will be asked to refrain from alternative treatment during the follow up period to allow the treatments to achieve their maximum effect. Patients randomized to the WL condition will not enter the post-treatment period. Instead, following a post-WL assessment, they will be offered treatment at CARD. Patients who wish to discontinue their participation in the study at any point or who wish to receive alternative treatment will be referred for clinical treatment.

Study Terminations. Every effort will be made to keep patients in the study for the full duration of the trial. Patients dropping out of the trial will be included in the data analysis as described in the Data Analysis Section. Patients will be instructed not to initiate any psychotropic medications or other psychological interventions during the course of treatment in order to “give treatment the best chance to work,” but patients will be removed from the study if, in the judgment of the therapist, clinical deterioration makes further participation ill-advised. In addition, patients may be withdrawn if they become ineligible for study participation (e.g., become medically ill or initiate alternative therapy). Patients withdrawn from the study for any reason will be offered alternative care or will be assisted to find other providers. Every effort will be made to record reasons for study dropout. Also, we will record the reasons that patients are excluded from or refuse to participate in the study in order to assess the possible impact this might have on generalizability of findings.

A.3. Materials and procedures

In our assessment battery we are trying to accomplish four things: (1) Select global measures of severity among all anxiety disorders that are sensitive to change and will serve as our primary outcome; (2) Select appropriate single-disorder measures that have been widely used in other studies to provide appropriate benchmarking comparisons for both principal and comorbid diagnoses; (3) Select assessments employing different methods (Independent Evaluator [IE] or clinician-rated as well as patient self-report) to provide converging lines of evidence; and (4) Select assessment time-points and measures that will allow evaluation of hypothesized mediators and mechanisms of change. Unless otherwise noted, instruments selected for this study have demonstrated clinical and research utility, are commonly used, and have reliability and validity data to support their use. Evaluating outcome for transdiagnostic treatment approaches poses a unique problem, namely, identifying well validated measures that provide adequate coverage of the core symptoms of anxiety disorders and are equally applicable across diagnostic categories. After careful consideration, we chose ADIS CSR ratings as the primary outcome measure for the study. ADIS CSR ratings provide a single dimensional scale ranging from 0 (no symptoms) to 8 (extremely severe symptoms) that is consistent across diagnostic categories and captures the degree of interference/disability the individual currently experiences as a result of his or her symptoms. While other measures might also satisfy these criteria, we have an extensive history administering the ADIS at our Center and have extensive reliability and validity data on this measure (Brown, 2007; Brown et al., 2001; Brown, DiNardo, Lehman, & Campbell, 2001). We will also use descriptive dichotomous algorithms of treatment response and high end-state functioning as utilized in our pilot study (see Ellard et

al., 2010) but these algorithms are not designated as a primary outcome measure for the purposes of this study.

Outcome measures are described below. In selecting assessment time-points for the present study, we attempted to strike a balance between adequate assessment spacing to test hypotheses about potential mediators of treatment outcome and patient burden. After careful consideration, we feel that the assessment timeline selected provides the optimal balance between assessment and patient burden. As is customary in these treatments, self-monitoring forms will also be used both as treatment elements and to assess the degree of change in the participants' symptoms. The timing and frequency of IE and questionnaire assessments are indicated in Table 1 below.

Table 1. Assessment Schedule

	TIME OF ADMINISTRATION			
	Baseline	Each Session	Sessions 4, 8, 12 & 16	Post-WL or Post-Tx
Interview Based Assessments				
Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994)	*			*
Mini-ADIS-IV (Brown, Di Nardo, & Barlow, 1994)			* ²	*
Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scale (SIGH-A and SIGH-D; Shear, Vander Blitt, & Rucci, 2001; Williams, 1988)	*			*
Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976)	*			*
Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989)	*			*
Panic Disorder Severity Scale (PDSS; Shear et al., 1997)	*			*
Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)	*			*
Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006)	*			*
Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, & Rothbaum, 1993)	*			*
Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973)	*		*	*
Diagnosis Non-specific Self-report Measures				
Beck Depression Inventory (BDI-II; Beck et al., 1996)	*			*
Beck Anxiety Inventory (BAI; Beck et al., 1988; Beck & Steer, 1990; Steer, Ranieri, Beck, & Clark, 1993)	*			*
Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006)	*		* ²	*
Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development)	*		* ²	*
Potential Mediators of Treatment Change				
Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)	*		* ²	*
Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004)	*		* ²	*
Behavioral Inhibition/ Behavioral Activation Scales (BIS/BAS; Carver & White, 1994)	*		* ²	*
Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985)	*		* ²	*
Emotion Regulation Questionnaire (ERQ; Gross & John, 2003)	*		* ²	*
Positive and Negative Affective Schedule - Global (PANAS-G; Watson, Clark, & Tellegen, 1988)	*		* ²	*
Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008)	*		* ²	*
Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development)	*		* ²	*
Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997)	*		* ²	*
Functional Impairment and Quality of Life				
Work and Social Adjustment Scale (WSAS; Marks, Connolly, & Hallam, 1973)	*			*
Rand-modified, Medical Outcomes Study 36-item Short-Form Health Survey (Rand-MOS-SF-36; Hays, Sherbourne, & Mazel, 1993)	*			*
Checklist of Emotional Avoidance Strategy Engagement (CEASE; Fairholme et al., under development)	*			*
Potential Moderators of Treatment Outcome				
Credibility/Expectancy Questionnaire (Devilly & Borkevec, 2000)	* ¹			
University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983)	*			
Other Measures				
Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986)		*		

1. Collected at the end of session two. 2. Collected at the start of session 1, and following sessions, 4, 8, and the last treatment session. Note: Treatment length will be 12 sessions for principal diagnoses of PD/A and 16 sessions for principal diagnoses of GAD, OCD, and SAD.

General IE Assessment of Severity of Symptoms and Functional Impairment Across All Principal and Comorbid Disorders

Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L; Di Nardo et al., 1994):

This semi-structured, diagnostic clinical interview focuses on DSM-IV diagnoses of anxiety disorders and their accompanying mood states, somatoform disorders, and substance and alcohol use. The information derived from the interview using the ADIS allows clinicians to determine differential diagnoses and gain a clear understanding of the level and severity of each diagnosis. Principal and additional diagnoses are assigned a clinical severity rating (CSR) on a scale from 0 (no symptoms) to 8 (extremely severe symptoms), with a rating of 4 or above (definitely disturbing/disabling) passing the clinical threshold for DSM diagnostic criteria. Inquiries about suicidal ideation are part of this interview. This measure has demonstrated excellent to acceptable interrater reliability for the anxiety and mood disorders (Brown, Di Nardo, et al., 2001). The full ADIS-IV-L (focusing on current and lifetime diagnoses) will be administered only at the original intake. During treatment and the follow-up period, we will administer

specific sections taken from an abbreviated version of the ADIS, focusing only on current symptomatology (*Mini-ADIS-IV; Brown, Di Nardo, & Barlow, 1994*) and corresponding to those disorders identified at the initial intake, following a strategy used for decades in clinical trials at out Center (Barlow et al. 2000). All ADIS interviewers at CARD are trained to a very high level of reliability and undergo a rigorous certification process (see Brown, Di Nardo, et al., 2001). In addition to the training procedures, study staff hold weekly meetings during which all initial diagnostic interviews conducted that week are discussed in the presence of senior clinicians, and in the instance of diagnostic disagreement, the sources of these differences are reviewed and a consensus diagnosis is reached. The staff meeting also reduces the potential for interviewer drift.

Psychiatric disorders will be assessed with the ADIS-IV diagnostic evaluation. Because the ADIS is routinely used for clinical and study evaluations at CARD, participants will have the option (see consent form) to consent for the use of a recent CARD evaluation for a repeated diagnostic evaluation in this study.

Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I; Guy, 1976): These widely used clinician-rated instruments assess global severity and improvement from pre-treatment baseline on 7-point scales. The CGI-I and CGI-S will be used to define clinical response. The reliability and validity of the CGI has been demonstrated among individuals with SAD (Zaider et al., 2003) and GAD (Lenze et al., 2009). At the comprehensive assessments, sections of the ADIS-IV (see above) will be used to assist in the determination of the CGI scores.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; Shear, Vander Bilt, & Rucci, 2001): The SIGH-A was developed to create a structured format for administering the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959). The SIGH-A includes specific instructions on administration and anchor points for assigning severity ratings. This measure demonstrated good inter-rater and test-retest reliability. In addition, scores are similar to (although consistently higher than) the HARS.

Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D; Williams, 1988): Similar to the SIGH-A, the SIGH-D was developed to provide more specific instructions for administration and scoring of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The SIGH-D also demonstrated good inter-rater and test-retest reliability and produces scores similar to the HRSD.

Work and Social Adjustment Scale- Clinician rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item descriptive measure assessing the degree of interference caused by the patient's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a valid, reliable, and change-sensitive measure that has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Specific IE Assessment of Single Principal and Comorbid Anxiety Disorder Diagnoses

Yale-Brown Obsessive Compulsive Scale Interview (Y-BOCS; Goodman, Price, Rasmussen, Mazure,

Delgado, et al., 1989; Goodman, Rasmussen, & Price, 1999): The Y-BOCS interview is designed to assess the presence and severity of OCD symptoms, including assessment of insight, avoidance, indecisiveness, perceived responsibility, slowness, pervasive doubting, global severity, and global improvement. The interview begins with a detailed checklist to inquire about obsessions and compulsions. From this 64-item checklist, patients are asked to select three main obsessions and compulsions, which are then evaluated in greater detail across five primary areas: time spent, interference, distress, resistance, and control. Items are scored on a 0 (none) to 4 (extreme) scale, yielding obsession and compulsion subscale scores (0-20) and a total score (0-40). The Y-BOCS interview has demonstrated excellent inter-rater reliability, good convergent validity, and is sensitive to treatment-related change (Goodman, Price, Rasmussen, Mazure, Fleischman, et al., 1989). Individuals receiving a diagnosis of OCD will be administered this measure to obtain an overall rating of OCD severity at baseline and at each subsequent major assessment.

Panic Disorder Severity Scale (PDSS; Shear et al., 1997): The PDSS is a seven-item scale providing ratings of the core features of panic disorder (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations) and the degree of work and social impairment/interference due to panic disorder. The PDSS has been shown to have good inter-rater reliability and good concurrent validity, and has been used successfully in treatment outcome research for patients with panic disorder with or without agoraphobia (Shear et al., 1997). Scores range from 0 to 21, with higher scores reflecting more severe panic symptomatology. Individuals receiving a diagnosis of PD/A will be administered this measure to obtain an overall rating of PD/A severity at baseline and at each subsequent major assessment.

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987): The LSAS is a 24-item scale widely used in the study of SAD. The LSAS was originally designed to assess the range of social interaction and performance situations that patients with SAD may fear and/or avoid (Liebowitz, 1987). Its 24 items are divided into two subscales that address social interaction (11 items) and performance (13 items) situations. The LSAS provides six subscale scores: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance. An overall total score can also be calculated by summing the total fear and total avoidance scores. The LSAS has been shown to have good internal consistency, is highly correlated with other measures of SAD, and is sensitive to the effects of treatment (Heimberg, et al., 1999; Safren et al., 1999). Individuals receiving a diagnosis of SAD will be administered this measure to obtain an overall rating of SAD severity at baseline and at each subsequent major assessment.

Generalized Anxiety Disorder Severity Scale (GADSS; Shear, Belnap, Mazumdar, Houck, & Rollman, 2006): The GADSS is a 6-item interview assessment that evaluates the core features of GAD. Modeled after the YBOCS and PDSS, the GADSS begins with a target worry list to identify situations that are the focus of worry (e.g., future, health, family, finances, and work). The remainder of the scale includes six items that evaluate core symptoms of GAD, including frequency of worry and associated symptoms, distress due to worry and associated symptoms, and impairment in social and work functioning. These items are rated on a 5-point scale, ranging from 0 (none) to 4 (very severe). The GADSS has been shown to have high internal consistency, good convergent validity, and appears to be sensitive to change in

treatment (Shear et al., 2006). Individuals receiving a diagnosis of GAD will be administered this measure to obtain an overall rating of GAD severity at baseline and at each subsequent major assessment.

Posttraumatic Stress Disorder (PTSD) Symptom Scale-Interview Version (PSS-I; Foa, Riggs, Dancu, &

Rothbaum, 1993): The PSS-I is a 17-item interview designed to assess current DSM-IV symptoms of PTSD. Each item, corresponding to the symptoms of PTSD, consists of one brief question that is rated from 0 (*Not at all*) to 3 (*5 or more times per week/Very much*). This measure yields a total PTSD severity score as well as reexperiencing, avoidance, and arousal subscores. The PSS-I has been shown to have high internal consistency and inter-rater reliability as well as good concurrent validity (Foa et al., 1993; Foa & Tolin, 2000). Individuals receiving a comorbid diagnosis of PTSD will be administered this measure to obtain an overall rating of PTSD severity at baseline and at each subsequent major assessment.

Self-Report Assessment of Severity of Symptoms of Depression and Anxiety

Beck Depression Inventory (BDI-II; Beck et al., 1996) and Beck Anxiety Inventory (BAI; Beck et al., 1988; Beck & Steer, 1990; Steer, Ranieri, Beck, & Clark, 1993): The BDI-II is a widely used measure assessing current depressive symptoms. It contains 21 items focusing on the levels of depressive symptoms over the past week. Participants are asked to circle the number next to the statement that best corresponds to how they felt over the past week. Scores range from 0 to 63, with higher scores indicating greater depressive symptoms. The BAI also contains 21 items scored in a similar way and focuses on common symptoms that are more unique to anxiety, such as somatic symptoms and certain cognitive symptoms.

Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein,

2006): The OASIS is a brief 5-item questionnaire that was developed as a continuous measure of anxiety related symptom severity and impairment that could be used across anxiety disorders, with multiple anxiety disorders, and with subthreshold anxiety symptoms. This measure has good internal consistency, excellent test-retest reliability, and convergent and divergent validity (Norman et al., 2006).

Overall Depression Severity and Impairment Scale (ODSIS; Barlow et al., under development): The ODSIS is a direct adaptation of the OASIS anxiety measure described above for depression. It is a brief 5-item questionnaire that assesses dimensional depression related symptom severity and impairment across depressive disorders and with subthreshold depressive symptoms.

Measures of Potential Mediators of Treatment Change

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986): The ASI is a 16-item questionnaire designed to assess fear of anxiety-related symptoms. The ASI has a high degree of internal consistency (Reiss et al., 1986) and stable test-retest reliability over a three-year period (Maller & Reiss, 1992).

Anxiety Control Questionnaire Revised (ACQ-R; Rapee, Craske, Brown, & Barlow, 1996; Brown, White, Forsyth, & Barlow, 2004): The ACQ-R is an 18-item measure designed to assess perceptions of control over potentially threatening internal and external events and situations associated with anxious responding. This measure has been shown to have good internal consistency and test-retest reliability (Rapee et al., 1996).

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS; Carver & White, 1994): The BIS/BAS is a 20-item self-report questionnaire designed to assess sensitivity to anxiety-provoking stimuli by tapping two alternative behavioral motivation tendencies – behavioral inhibition (BIS) and behavioral activation (BAS). The BIS/BAS has demonstrated good convergent and discriminant validity excellent reliability, satisfactory criterion and construct validity (Hazen, Walker, & Eldridge, 1996).

Eysenck Personality Questionnaire Revised – Short-Form (EPQR-S; Eysenck & Eysenck, 1975; Eysenck, Eysenck, & Barrett, 1985): The EPQR-S is a commonly used 48 item personality inventory consisting of four subscales of 12 items each: Extraversion, Neuroticism, Psychoticism, and a Lie scale. In this study, we will only be administering the Extraversion and Neuroticism subscales (24 items total). This scale has been shown to have good reliability and excellent validity (Brown, 2007).

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003): The ERQ is a 10-item self-report questionnaire that assesses individual differences in the dispositional tendency to employ two separate emotion regulation strategies – reappraisal and suppression. The scale has demonstrated high internal reliability and demonstrated strong convergent and discriminant validity (Gross & John, 2003).

Positive and Negative Affective Schedule – Global (PANAS-G; Watson, Clark, & Tellegen, 1988). The PANAS is a brief, reliable and valid measure of positive and negative affect. It consists of 20 feeling or emotion words (e.g., interested, upset, nervous). Respondents rate each emotion word on a scale ranging from 1 = very slightly or not at all to 5 = extremely, indicating the extent to which they experience that emotion or feeling in general. The PANAS-G has shown excellent convergent and divergent validity and is a widely used measure of state negative affect (Watson et al., 1988).

Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). The ERSQ is a 27-item self-report measure (originally developed in the German language, and translated into English) that assesses various emotion regulation strategies in both clinical samples (Berking, Wupperman, Reichardt, Pejic, Dippel, & Znoj, 2008) and community samples (Berking & Znoj, 2008). The ERSQ has displayed sensitivity to patients undergoing psychological treatments (Berking & Znoj, 2008; Berking et al., 2008) as well as at-risk samples (i.e., police officers) who participated in emotion regulation training (Berking, Meier, & Wupperman, 2008).

Emotional Avoidance Strategies Inventory (EASI; Fairholme et al., under development). The EASI is a 33-item self-report questionnaire that assesses individual differences in the dispositional tendency to avoid, attenuate and reduce emotional experiences. The scale is currently under development. Items were generated using existing scales that are widely used in research and clinical practice, including the DERS, ERQ, TMMS, and the AAQ. Items were adapted to make them directly relevant to avoiding emotions. For instance, the item “If I find myself getting mad, I try to calm myself down” from the TMMS, was changed to read “I try hard to calm myself down when I find myself getting angry.”

Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997). The ACS is a 42-item self-report measure designed to assess fear of loss of control when experiencing strong affective states. ACS subscales expand on the construct of fear of fear, including *fear of anxiety*, *fear of depression*, *fear of anger*, and *fear of strong positive affective states*. The ACS has demonstrated acceptable internal consistency, test-retest reliability, and convergent and divergent validity (Berg, Shapiro, Chambless, & Aherns, 1998; Williams et al., 1997).

Measures of Functional Impairment and Quality of Life

Work and Social Adjustment Scale – Self Rated (WSAS; Marks, Connolly, & Hallam, 1973): The WSAS is a five-item measure asking participants to rate the degree of interference caused by their symptoms in work, home management, private leisure, social leisure, and family relationships. Interference is rated over the past week on a 0 to 8 scale (0 = not at all interfering to 8 = severe interference). The WSAS is a descriptive measure of subjective interference in various domains of living, and has been successfully used in several previous studies (e.g., Brown, Antony, & Barlow, 1995).

Rand-modified, Medical Outcomes Study 36-item Short-Form Health Survey (Rand-MOS-SF-36; Hays, Sherbourne, & Mazel, 1993): The Rand-MOS-SF-36 (Ware & Sherbourne, 1992) is a well-validated, comprehensive, self-administered instrument that is widely used in medical and psychiatric settings to provide a multi-dimensional assessment of mental and physical health-related status. The SF-36 measures 8 health related dimensions: physical functioning, bodily pain, role limitations due to physical health problems, general mental health, social functioning, energy/fatigue, and general health perceptions. The Rand-modified version of the SF-36 consists of identical items and scales but is scored differently and includes two factor analytically derived physical and mental health composite scores.

Checklist of Emotional Avoidance Strategy Engagement (CEASE; Fairholme et al., under development). The CEASE is a self-report questionnaire that was developed by the authors of the Unified Protocol assesses the frequency and severity of common emotional avoidance strategies (Barlow et al., 2008). It contains 68 checklist items of common emotional avoidance strategies followed by 6 supplemental questions which assess overall severity and interference due to use of these avoidance strategies. Some items were developed based on items of the Texas Safety Maneuvers Scale (TSMS; Kamphuis & Telch, 1998) and others were developed and agreed upon by a group of experts in the area of emotional disorders. Validation for the CEASE is currently ongoing.

Measures of Potential Moderators of Treatment Outcome

In addition to demographic characteristics (gender, age, ethnicity, marital status, education, employment), and pre-treatment scores on various assessment measures, the following measures will be explored as potential moderators of response to treatment and maintenance of treatment gains during the follow-up period.

Credibility/Expectancy Questionnaire (Devilley & Borkovec, 2000): This revision of the Borkovec and Nau (1972) Credibility Questionnaire now has 2 psychometrically confirmed factors, credibility of the treatment rationale and expectancy for improvement. This scale will be administered at the end of the second session in order to determine whether patients view the therapy as sufficiently credible, and whether it evokes significant expectancy for change. Data from this scale will be compared to existing norms from published clinical trials for well-established treatments.

University of Rhode Island Change Assessment (URICA; McConaughy, Prochaska, & Velicer, 1983): The URICA is a 28-item self-report measure developed to evaluate the process of change in therapy. This measure has been used extensively in the area of substance use (e.g., Project MATCH Research Group, 1997) and more recently in anxiety disorder populations (Dozois, Westra, Collins, Fung, & Garry, 2004). The URICA assesses patient's stage of readiness to change in treatment.

Measures of study integrity

Homework Compliance Scale (Primakoff, Epstein, & Covi, 1986): At the end of each session, the therapist will evaluate the degree of homework compliance for each patient by a 0-6-point compliance scale. Following the procedure by Leung and Heimberg (1996), an overall average rating will be obtained for each patient by summing the scores for all sessions and dividing them by the number of sessions attended.

Self-monitoring

In addition, a variety of self-monitoring forms that are integral to most cognitive behavioral approaches to emotional disorders will be utilized for treatment purposes and may yield quantifiable data across subjects. These included standardized forms for automatic thoughts, avoidance, interoceptive and situational exposure, and emotion (e.g., weekly record of anxiety and depression, see Barlow & Craske, 2000; Barlow, Rapee, & Reisner, 2001; Craske, Barlow, & O'Leary, 1992).

Quality Control

Checks on the Integrity of Assessment Procedures. All clinician-rated assessments will be conducted by IEs who are blind to treatment assignment. We have previously established that double blind procedures are often not completely effective in protecting IEs from accurate guessing of treatment condition (Roll et al., 2004). Based on this knowledge, we will implement all of the steps recommended by Roll et al. (2004) to reduce the occurrence of providing inadvertent clues to treatment assignment and to protect against the impact of possible systematic bias in the responding of IEs. The IEs for the proposed study will be Ph.D. or near-Ph.D. level diagnosticians who have previous research experience with structured interviewing and who will receive additional training and certification for this study under the direction of Drs. Barlow, Farchione, and Brown. A two-level system will be used to maintain the reliability of diagnoses and prevent drift in other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected recordings of clinical assessments. Each month an IE will

listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments. These duplicate ratings will be used both to calculate kappa coefficients and for supervision. Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help to ensure that IEs refine their diagnostic skills and will also establish common guidelines for ongoing use in diagnostic decision-making. Inter-rater agreement will be assessed via evaluation of digital recordings of diagnostic interviews (as described above). Inter-rater reliability (kappa) will be calculated for each of these diagnostic categories: PD/A, SAD, GAD and OCD.

Training, Certification, and Supervision of Study Therapists. UP and SDP therapists will be experienced clinicians who have undergone training and certification in the treatment protocols utilizing procedures employed in clinical trials at CARD over the last 20 years (e.g., Barlow et al., 2000). To reduce allegiance effects, therapists will be trained in either the UP or SDPs and will be dedicated to administering this treatment approach (UP or SDPs) for the duration of the study. Training will be done by experts from CARD under the direction of Drs. Barlow, Farchione, and Murray. The training procedures will consist of didactic instruction and hour-for-hour supervision on one of two concurrent training cases. Therapists-in-training will attend group supervision meetings, at which both specific application and general issues of these protocols will be discussed. Trainees who have had previous supervised experience with the treatment protocols will not need to complete training cases before starting the certification process.

The certification procedures will consist of systematic review of digital recordings of one therapy case treated after the initial two training cases. Using similar procedures and scales to those currently employed across treatment outcome studies, certification for UP therapists will be completed by expert therapists at CARD and overseen by Drs. Barlow and Farchione, while certification for SDP therapists will come from experts from the team of the treatment originators: for PD/A and GAD, Dr. Michelle Craske; for SAD, Dr. Debra Hope; and for OCD, Dr. Gail Steketee. The scales are designed to assess four aspects of the therapist's conduct of psychotherapy: adherence to the treatment protocol, avoidance of proscribed interventions, skill in administering treatment components, and general therapeutic skill (e.g., attending to signs of disruption of the therapeutic alliance). To be certified, the therapist must achieve a cut-off score of 5 (range 1 to 7) on all scales across at least 75% of sessions per case. Trainees who do not meet those criteria may be given additional training consisting of hour-for-hour supervision of another case and will try for certification again on another unsupervised case.

Checks on the Integrity of Treatment Procedures. Consistent with the procedures for maintaining the integrity of the diagnostic and clinical assessments, the quality of study treatments will be assured by ongoing supervision and reviews of approximately 20% of randomly selected session recordings, following long-standing practices in clinical trials at our Center.

Data Collection

Participants will be asked to complete study questionnaires using a computerized data collection program. Participants who have difficulty using the online data collection program, or feel uncomfortable using this method of data collection, will have the option to complete study questionnaires in a paper-and-

pencil format. Data from these questionnaires will then be entered by study personnel using the online data collection platform.

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and *p* value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

B. Selection criteria

Participants will be recruited from among individuals presenting for treatment at CARD. After the usual clinical screening at CARD where the eligibility of the patient will be ascertained, potential participants would meet with a study clinician to review study procedures including the nature of treatment, the potential for a sixteen week delay in treatment if they are randomized to the waitlist, and to

answer any questions. Discussion will include information about the treatment options along with a brief rationale for these approaches. Participants will be informed about the nature of the waitlist condition, including their ability to receive their choice of the active treatments following their study participation and invited to ask questions which will be answered by the project staff member. Patients will be informed of the nature of the investigation, the types of assessments and treatments involved, and the potential risks involved in participation; they will be asked to sign an informed consent statement prior to participating in the research project. Anybody is free to decline participation in the study and would then be assigned to the clinic waitlist for usual and routine treatment. Male and females, ages 18 years or older, who have received a DSM-IV principal diagnosis of SAD, PD/A, GAD, or OCD as determined by their initial CARD assessment will be eligible to participate in the study. Interested participants will be given information about the nature of the study over the telephone and will undergo an initial screening to determine their eligibility. Patients will then complete a pre-treatment assessment before being randomized to study conditions. A minimum of 50 patients from each of the 4 principal diagnostic categories, SAD, PD/A, GAD, or OCD, will be included in the randomization to ensure adequate representation of each anxiety disorder.

Inclusion criteria. Individuals will be eligible for participation in this study if they are 18 years or older; are assigned a principal diagnosis of SAD, PD/A, GAD, or OCD as determined by a clinician-administered diagnostic assessment using the Anxiety Disorder Interview Schedule for *DSM-IV* (ADIS-IV; Di Nardo, Brown, & Barlow, 1994; see description below); and are rated as crossing the threshold for a formal DSM-IV diagnosis by assignment of an ADIS clinical severity rating (CSR) of 4 (definitely disturbing/disabling on the 0-8 CSR scale) or higher on at least the principal diagnosis. Following long-term conventions in prior studies, a principal diagnosis is operationally defined as the disorder causing the most severe current impairment and/or distress in instances where the patient meets criteria for 2 or more current diagnoses. The remaining diagnoses are classified as additional (comorbid) diagnoses. Conditions meeting diagnostic criteria at CSRs of 3 or less are categorized as subclinical. Patients with comorbid diagnoses, including all anxiety disorders and depression, will be included. Rarely, co-principal diagnoses are assigned if both disorders are determined to cause equal levels of impairment and/or distress. In these cases, both diagnoses must be from the four anxiety disorders listed above. In addition, to be eligible for participation, individuals must be willing to be randomly assigned to treatment conditions and willing to refrain from initiating additional treatment during the course of treatment.

Exclusion criteria. In order to maximize generalizability, exclusion criteria are based solely on the well-being of the patient and will consist primarily of those existing conditions that in a clinical context would require prioritization for immediate treatment, thereby delaying treatment for anxiety, or requiring simultaneous treatment which would interact with study treatments in unknown ways, including: (a) current *DSM-IV* diagnoses of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder; (b) clear and current suicidal risk; and (c) current or recent (within 3 months) history of substance abuse or drug dependence. Individuals will also be excluded if they previously received an adequate trial of CBT or if their emotional symptomatology is due to a medical/physical condition, in which case alternative treatment would be clinically indicated. Following long-standing procedures at CARD, patients on psychotropic medications will be included if they are willing to maintain a stable dosage throughout treatment. This avoids problems with reluctance to discontinue or difficulty with discontinuing, but also the confounding of outcomes assessment from initiation of medication during treatment. In practice this strategy has worked well through many clinical trials over the last 15 years.

C. Information Provided to Subjects

General information about the study will be provided at the telephone screening and a more detailed description of all study procedures will be given during the informed consent process. Please see the consent form for a description of the detailed information that will be provided to patients prior to being enrolled in the study. Information contained in the consent form will be verbally reviewed with the patient prior to obtaining written consent, and any questions regarding the study procedures will be addressed at that time. More specifically, members of the study staff will review all areas of the consent form, including: 1) the purpose and duration of the study; 2) assessment and treatment procedures; 3) risks and benefits; and 4) issues related to confidentiality. Patients will be informed that participation in the study is voluntary and that they have the right to withdraw from the study at any time without penalty.

D. Informed Consent

Following the initial diagnostic interview conducted at CARD, patients who are potentially eligible for the study (meet all study inclusion criteria) will be contacted by phone for a brief telephone screening. Patients who are interested in participating will be scheduled for a brief meeting where the potential participants will be asked to read and sign an informed consent form for study participation. After reading the forms, the participant will be encouraged to ask any questions. Next s/he will sign the forms if agreeing to participate. Participants will be provided with copies of the signed consent forms for their records.

E. Expected Benefits

Patients will receive free, individual treatment with an experienced clinician for their anxiety concerns. Patients will also be compensated a flat rate of \$50.00 per completed assessment. For those patients who have missed or have been unable to be reached for their previous appointment we will adjust from a flat rate of \$50.00 per completed assessment to increasing the possible reimbursement amount. A total of \$150.00 can be earned for completing all scheduled assessments. Additionally, we will offer parking vouchers to patients, as needed, to help defray any costs they may otherwise incur while traveling to our center to complete scheduled assessment appointments. We will provide up to four parking vouchers (which cost approximately \$6.00 each) to each participant for completion of study assessments.

Potential benefits to psychological/scientific knowledge include the possibility of developing a single treatment protocol that is applicable to a variety of anxiety disorders. This would increase dissemination and effective training of clinicians in the “real world” who would not typically have access to such treatments. This project will also add to the knowledge of anxiety and emotional disorders by highlight the underlying bases of anxiety disorders and emotional processes. The potential benefits to society include decreased costs related to utilization of services due to anxiety disorders. Results of this study will expand knowledge of anxiety disorders by providing an effective treatment based on common processes.

F. Potential Risks

As with any assessment procedure patients may experience some anxiety and or distress during the assessment. It is also possible that certain practices during the course of treatment may elicit anxiety or discomfort. It is also possible that patients assigned to the wait-list condition may experience some deterioration in their symptoms prior to receiving their intervention. In addition, although the treatment is likely to alleviate many of the symptoms and interference from anxiety, the success of treatment cannot be guaranteed for any particular individual.

Minimization of risks

The following procedures will be used to minimize risks for participants:

134. Several aspects of the research plan are intended to minimize the risk to participants. First, both the Center and the study exclusion criteria exclude any patients who are currently experiencing clinical levels of suicidal ideation. In addition, the study will also exclude individuals who require a higher level of care and/or more intensive treatment than is offered by the study. Research staff will closely monitor individuals in the waitlist condition to ensure that their condition does not deteriorate significantly. Should this happen, the PI or Dr. Farchione will reevaluate the patient and either begin the study treatment immediately, or provide a referral for immediate treatment (e.g., pharmacotherapy, additional psychotherapy, inpatient treatment). Moreover, the research staff will closely monitor the suicide item on the Beck Depression Inventory. If, at any time, a participant indicates a score >1 on this item, he or she will be immediately reevaluated by the PI or co-PI and referred for immediate treatment, if necessary.
135. The PI and Dr. Farchione will conduct regularly, weekly meetings with research staff as well as weekly supervision meetings with study therapists. At these meetings, any concerns regarding patient safety (e.g., suicidal ideation) will be fully discussed, and the PI or Dr. Farchione will intervene as clinically indicated.
136. All assessment and treatment procedures will be conducted by trained and experienced clinicians. Doctoral students, postdoctoral fellows, and clinical psychologists will be working under the direct supervision of licensed psychologists at CARD. Up until the time of consent, these screening procedures are the usual and customary clinical intake procedures at CARD.
137. Treatment will be closely monitored by licensed clinical psychologists on the study staff in weekly supervision meetings. Any patient showing significant deterioration or developing active suicidal potential as judged clinically by the treating therapist and a licensed supervisor will be removed from the structured protocol and given immediate and intensive clinical intervention as per usual procedures at CARD. The PI will review any adverse events which occur during the course of the study.
138. Patients on the waitlist will wait approximately four months, but the current wait list at CARD ranges from two to five months so this will not be an undue burden. In addition, we will actively monitor patients randomized to the wait list and will contact them about half way through their wait for assessment. Any patient undergoing some deterioration or developing active suicidal potential who had not previously reported problems would be removed from the study and provided with immediate clinical intervention or appropriate referral.
139. If any patient's condition does not improve after completing the study s/he will be offered further treatment for a maximum of 12 sessions at the Center, which will be free of charge or provided with an appropriate referral to another clinician or clinic.
140. Finally, all patients will be clearly informed of their right to withdraw from the study at any point.

Risk/benefit ratio

The risks involved in this study are no greater than those associated with therapy in general or usual and customary treatment at CARD. Once again, the wait for patients randomized to the wait list is not unduly long. In addition, all patients randomized to this study will be offered free treatment as compared to usual sliding scale fee in effect at CARD for clinical treatment. The risk of some increased anxiety during assessment and treatment is more than offset by the potential benefits of long-term reduction in symptoms of emotional disorders, particularly since all of the elements in these treatments have been empirically supported in previous studies. In addition, patients will earn \$50 for completion of post treatment and follow-up assessment batteries.

Data safety and monitoring plan

The following procedures will be followed, in compliance with NIH requirements to ensure the safety of study participants and the validity and integrity of data. For this study we will utilize a Data and Safety Monitoring Board (DSMB). The DSMB will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support these purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality, and will monitor enrollment to ensure that the study conclusion is not delayed.

To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of the career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for mental disorders, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. The three members will be Drs. Brett Liz, John Otis, and Tibor Palfai. The Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a yearly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.
2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but also other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for dropout.
3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. All relevant information will be reported to the DSMB for each SAE including

information about the event and its outcome, concomitant medications, and the subject's medical history and current conditions. Reporting to local IRBs will be completed within 24 hours of the SAE. Notification by e-mail shall be made to the DSMB within 7 days of the occurrence of any SAE.

4. Non-Serious Adverse Events – At yearly intervals during the course of the study and then again at its completion, the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.
5. Other Safety-Related Reports – At yearly intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.
6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

At least on an annual basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

G. Confidentiality

Any information that is obtained in connection with the study will remain confidential and will not be released without written permission. Confidentiality will be maintained by the following means:

- Participants will be identified using a subject screening number. This number will be used on all study forms and data. Individual identifiers will be contained in a source binder.
- Study files will be kept in locked binder storage cabinets.
- Electronic data will be stored on computer disks that will be kept in a locked cabinet in a restricted area. Printed data will be stored in restricted areas and archived in locked cabinets. Only study personnel will have access to locked cabinets where electronic and printed data are kept.
- Twenty percent of study treatment sessions will be digitally recorded for the study's expert raters to assess therapist adherence to specific treatment guidelines. Treatment sessions will not be

recorded if the patient has not consented in writing to the recording. Session recordings, like all study data, will only be identified by the subject's screening number. No personally identifying information will be included on session recordings.

- Any electronic data collected online or stored on a secure server will be encrypted and password protected. This will restrict access to the data by anyone other than research personnel.
- Any digital audio recordings of treatment sessions that are temporarily maintained on a secure server will be accessible only by select, authorized members of the research team responsible for treatment certification and adherence. Only a limited number of files will be made available at a given time and once these files are reviewed, they will be promptly removed from the server.
- All study staff are required to have training and certification in Protecting Human Research Participants from the NIH Office of Extramural Research.

8. Informed Consent Form(s).

Two copies of the informed consent form are attached.

I accept responsibility for assuring that this study will be carried out in accordance with all applicable federal state and local laws and regulations and in accordance with the policies of Boston University, with respect to the protection of human subjects participating in this study.

Signature of Principal Investigator Date

This application has been reviewed and approved for submission to the Charles River Campus IRB.

Chairman/Director of Department Date

Data Analysis

Many hypotheses will be addressed by latent growth models (LGM) that will be analyzed using Mplus 5.2 (Muthén & Muthén, 1998-2009). To avoid redundancy in subsequent sections, a brief overview of the data analytic plan is provided here. Initially, the assumption of multivariate normality in the data will be examined to determine the most appropriate minimization function. Normality and outlier analyses will be conducted using Mardia's index of multivariate kurtosis (cf. Bentler, 1995). If multivariate normality appears to be problematic, robust maximum likelihood estimation (Bentler, 1992) will be used (cf. Brown, 2006). If the data are approximately multivariate normal, the maximum likelihood (ML) estimator will be used. Missing data will be accommodated in the analyses using direct ML (or multiple imputation in the case of Aim 1 analyses), under the missing at random (MAR) assumption (cf. Allison, 2003; Brown, 2006). In addition to fostering statistical power, modern missing data methods such as direct ML and multiple imputation provide accurate parameter estimates and standard errors, unlike traditional methods such as listwise deletion (restricting analyses to completers only) or intent-to-treat (ITT) analyses where the last observation is carried forward (cf. Schafer & Graham, 2002). Additionally, the distinction between ITT and completer analyses becomes artificial, because the study analyses include all cases that are randomized into the trial, including individuals who drop out of treatment. The LGM models will be fit to the data and descriptive goodness of fit will be evaluated using the fit statistics and associated cutoff guidelines proposed by Hu and Bentler (1999): χ^2 , standardized root mean square residual (SRMR; close to .08 or below), root mean square error of approximation (RMSEA, close to .06 or below; 90% confidence interval and p value of RMSEA for test of close fit); Tucker-Lewis index (TLI) and comparative fit index (CFI) (both CFI and TLI: close to .95 or above). Although the CFI is one of the better behaved indices of fit available (Bentler, 1992, 1995), multiple indices will be used because this strategy provides a conservative method of evaluating fit and because each index provides different information regarding the degree of fit (Brown, 2006; Jöreskog, 1993). Fit diagnostics will be examined carefully (standardized residuals, modification indices) to determine any focal points of strain in the models. If necessary, modifications to the models will be made and the new model will be re-estimated and evaluated with the data. Formal comparisons with the initial model will be made using nested χ^2 methodology, where appropriate. In instances where an estimator other than ML is employed, the appropriate scaling corrections will be incorporated to yield the proper χ^2 difference test (e.g., under robust ML, the simple χ^2 difference of nested models does not follow the χ^2 distribution; cf. Brown, 2006).

Hypothesis 1. To test the hypothesis that UP will be statistically equivalent SDPs, we will compare the magnitude of the acute treatment effects of UP and SDPs using equivalence analysis. Equivalence analysis demonstrates statistical equivalence by evaluating the null hypothesis that the two treatments significantly differ from one another (Blackwelder, 1982). Statistical equivalence is defined as indicating no clinically meaningful difference in the efficacy between treatments based on criteria specified *a priori*. Statistical equivalence will be determined using a two one-sided confidence interval approach (Bristol, 1999). The minimum

value where one would prefer one treatment over another, called delta (δ), is selected *a priori* and the observed difference between the two treatments is compared against this value. The two treatments are determined to be equivalent if the entire confidence interval for the observed mean difference between the two treatments falls within the zone of equivalence ($-\delta, +\delta$). The null hypothesis of non-equivalence between two treatments can be expressed as two one-sided confidence intervals: $H_0: \mu_E - \mu_C \leq -\delta$ and $H_0: \mu_E - \mu_C \geq \delta$ versus $H_1: \mu_E - \mu_C > -\delta$ and $H_1: \mu_E - \mu_C < \delta$ where μ_E is the mean pre- to post-treatment change for the experimental group and μ_C is the mean pre- to post-treatment change for the control group. Thus, the choice of delta is critical for conducting equivalence analysis and requires a delicate balance between clinical and practical considerations. Following the recommendations of Wiens (2002), we selected a delta value of 0.75 CSR for the ADIS as we determined that this difference or less would not represent a clinically meaningful difference between two treatments that would lead us to prefer one over the other. As noted in the Introduction, we determined that the 1 unit CSR change on the ADIS at post-treatment designated as delta in the previous application is associated with changes of 0.81 and 0.85 units at post-treatment on the HAM-A and HAM-D respectively ($r_s = .67$ and $.78$, both $p_s < .001$). Consultation of meta analysis of existing treatment outcome studies suggests that SDPs are typically associated with 4.34 and 3.70 unit differences (HAM-A and HAM-D, respectively) at post-treatment relative to credible active comparison conditions (see Hofmann & Smits, 2008). With the deletion of the paroxetine condition, we were able to increase the sample size in each of the remaining active treatment conditions (UP and SDPs) in order to reduce our *a priori* delta value from 1 to 0.75 CSR, offering a more stringent test of equivalence. Hypothesis 1 is equivalent to $-\delta < Y_{UP} - Y_{SDP} < \delta$ where Y_{UP} is the mean pre- to post-treatment difference for UP and Y_{SDP} is the mean pre- to post-treatment difference for SDPs. Consistent with recommendations from Rogers, Howard, and Vessey (1993), when statistical equivalence is not obtained, we will follow up with traditional tests for mean differences (e.g., independent sample t-tests) to determine whether the treatments significantly differ from one another.

Hypotheses 2a and 2b. The hypothesis that UP and SDPs will have superior acute efficacy than WL will be evaluated by conditional LGMs. Using primary measures as outcomes (e.g., ADIS CSR), the intercept of the LGM will be centered on pre-treatment (i.e., first slope loading will be fixed to 0.0). Because there is no substantive interest in the form of the growth trajectory, slope factor loadings for mid-treatment assessments will be freely estimated and the final timepoint of interest (e.g., post-treatment) will have a corresponding factor loading fixed to 1.0. Accordingly, the mean and variance of the slope will convey the fixed (average) and random effects (individual differences) of change for the given time interval of interest. Treatment condition (dummy codes using WL as the reference group) will be included as a predictor in the model to account for individual differences in acute symptom reduction due to treatment assignment. A significant Treatment Condition \times Slope path reflects an interaction effect (i.e., the effect of Time on the outcome measure is moderated by treatment condition). The nature of these LGM interaction effects will be characterized using the procedures described by Curran, Bauer, and Willoughby (2004) (for an applied example, see Brown, 2007).

Power Analyses. All sample size estimates were based on conventional target values of power = 0.80 and alpha = 0.05. The power calculations were conducted for tests of the hypotheses for specific aims 1 and 2 and were conducted using SAS PROC POWER (SAS Institute, 2003). ADIS CSRs for the principal diagnosis were used as the primary outcome for all power analyses. Power calculations for the equivalence analysis test of hypothesis 1) UP and SDPs and hypothesis were conducted using delta estimates of 0.75 CSR for the ADIS. Based on the observed post-treatment standard deviation (*SD*) from our previous studies using the UP (Ellard et al., 2010), we estimated the *SD* for these comparisons of the ADIS to be 1.66. Assuming a sample size of 91 per group, then we will be able to detect (with power = 0.80) equivalence (zone of equivalence -0.75, 0.75). To be conservative we added 10% to the minimum required sample size, thus $n = 100$ for active treatment groups.

Power calculations for the superiority analysis tests of hypothesis 2a) UP and WL and hypothesis 2b) SDPs and WL were conducted using an allocation ratio of 2 for active treatment to WL groups. Unequal treatment allocation can increase the power and efficiency of a design, especially when one of the comparison groups is a placebo control condition (Woods et al., 1998). Following the methods described by Woods et al (1998), the sample size for WL was determined using $n=100$ for the active treatment conditions and a harmonic mean=66 (harmonic mean selection was based on the sample size needed to detect a moderate effect size at power=0.90). Using the harmonic mean equation provided in Woods et al. (1998) and solving for the required sample size for the third group (WL) provided a necessary sample size of 50 to achieve power=0.90.