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GATE: GENERALIZED ANXIETY – A TREATMENT EVALUATION

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LIST OF ABBREVIATIONS

AE	Adverse Events
AIC	Akaike Information Criterion
BAI	Beck Anxiety Inventory
BASC	Behavior Assessment System for Children
BDI	Beck Depression Inventory
BIC	Bayesian Information Criterion
BU	Boston University
CAM	Complementary and Alternative Medicine
CAMM	Child Acceptance and Mindfulness Measure
CARD	Center for Anxiety and Related Disorders
CATSD	Center for Anxiety and Traumatic Stress Disorders
CBT	Cognitive Behavioral Therapy
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression - Severity Scale
COPD	Chronic Obstructive Pulmonary Disease
DSMB	Data Safety and Monitoring Board
DSMP	Data Safety and Monitoring Plans
DSM-V	Diagnostic Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic Statistical Manual of Mental Disorders, Fourth Edition
ECG	Electrocardiogram
EDC	Electronic Data Capture
FFMQ	Five Facet Mindfulness Questionnaire
FU	Follow-Up
GABA	Gamma-amniobutyric Acid
GAD	Generalized Anxiety Disorder
GLMM	General Linear Mixed Models
HIPAA	Health Insurance Portability and Accountability Act
HARS	Hamilton Anxiety Rating Scale
MGH	Massachusetts General Hospital
ICC	Intraclass Correlation Coefficient

IE	Independent Evaluators
IRB	Institutional Review Board
ISI	Insomnia Severity Index
MCQ	Meta-cognition Questionnaire
MD	Doctor of Medicine
MOCA	Montreal Cognitive Assessment
MPAI	Music Performance Anxiety Inventory
MRM	Mixed-effects Regression Model
NCCAM	National Center for Complementary and Alternative Medicine
NIH	National Institute of Health
NYU	New York University
NYULMC	NYU Langone Medical Center
OHRP	Office for Human Research Protections
PAQ	Performance Anxiety Questionnaire
PCP	Primary Care Physician
PI	Principal Investigator
POMS	Profile of Mood States
PSQI	Pittsburgh Sleep Quality Index
PSQW	Penn State Worry Questionnaire
PSS	Perceived Stress Scale
QOL	Quality of Life
RCT	Randomized Control Trial
RN	Registered Nurse
RSA	Respiratory Sinus Arrhythmia
SAE	Serious Adverse Events
SCID	Structured Diagnostic Interview
SCL-90-R	System Check List version 90 revised
SE	Stress Education
SES	Socioeconomic Status
SIGH A	Structured Interview Guide for Hamilton Anxiety Scale
SOCID	Social Identification Scale
STAI	State-Trait Anxiety Inventory

PRÉCIS

Study Title

Yoga for generalized anxiety disorder: A comparison between yoga, cognitive behavioral therapy, and stress education training

Objectives

The general purpose of the study is to determine whether yoga is an effective method for treating GAD, and its relative efficacy compared to a standard psychosocial intervention. Our primary objective is to examine the short-term treatment efficacy of yoga on GAD symptoms. Our secondary objective is to examine the long-term treatment efficacy of yoga on GAD symptoms. Our tertiary objective is to examine and compare the mechanism of treatment changes in yoga and traditional CBT for GAD.

Design and Outcomes

This five-year multi-site study will examine the comparative efficacy of yoga, CBT, and stress education, a previously employed control condition, for patients with GAD. Across 2 enrolling centers (BU and MGH) we will randomize 230 patients with GAD to one of three 12 session weekly study treatments: 12-weekly yoga (n=95), CBT (n=95), or stress education (SE: n=40). Independent clinical assessments will occur before the 12-session intervention phase, at mid-treatment, after the intervention, and at 6-month follow-up. All clinician-rated outcomes will be assessed by trained Independent Evaluators (IEs) blind to treatment assignment. Response (CGI-I of 1 or 2) will serve as the primary outcome measure alongside the SIGH A as the core secondary continuous measure. Secondary outcome measures also include the STAI, PSS, BDI-II and BAI, QOL, ISI, PSQI and PSWQ. The FFMQ, MCQ, pre-ejection period, and cortisol are examined as possible mediators of change. The Credibility/Expectancy Questionnaire will be administered to examine whether credibility and expectancy moderates therapy outcome. In addition, we will explore whether clinical characteristics (comorbid diagnoses) and demographic characteristics (age, sex, SES) are possible moderators. We hypothesize that Yoga and CBT will each be superior to SE at post-treatment FU, and Yoga and CBT will not differ based on equivalency analyses. We predict that treatment changes during yoga are mediated via changes in mindfulness and changes in vagal tone, whereas changes in CBT are mediated via changes in maladaptive cognitions.

Interventions and Duration

The interventions include 12-week yoga, CBT, or stress education sessions. Independent clinical assessments will occur before the 12-session intervention phase, at mid-treatment, after the intervention, and at 6-month follow-up. We will allow a maximum of one month for the time between baseline assessment of participants and randomization; should more than one month pass for logistical reasons, baseline psychological assessments would be repeated prior to randomization. Once participants complete eligibility and are randomized to a group, they will start treatment within 4 weeks.

All 3 treatments will be administered in a group format to better reflect the most commonly available yoga format, and to maximize feasibility and cost-effectiveness (see also Integrity of Treatment Procedures). Providing all 3 modalities in the same sized and length group format will also maximize integrity for the comparison of the active treatment components. All three treatments will be 2 hours in duration, allowing for 15 minutes of study logistics including

discussion of subject questions or difficulties with the home or group interventions, evaluation of individual subject compliance, and strategizing enhancing compliance. The treatment itself will comprise a full 105 minutes training and practice in each group session. Subjects in all 3 treatment groups will be provided with a credible rationale for the efficacy of their assigned treatment. Subjects in the CBT arm will be informed of the role of CBT in the efficacy of changing dysfunctional thought patterns and beliefs, subjects in the yoga arm will be informed of the role of yoga in changing cognitive and physical emotional and stress reactivity through the postures, breath regulation and meditation components of yoga practice, and subjects in the Stress Education class will be informed about a variety of topics on stress and well-being: stress theory and physiology, effects of stress on body systems including cardiovascular and immunological, sleep efficiency, time management, nutrition, and exercise.

Sample Size and Population

We will randomize 230 patients with a primary diagnosis of GAD. Yoga (N = 95) will be compared to SE (N = 40), a commonly used control condition, and standard CBT for GAD (N = 95). All interventions will be conducted in a group format over 12 weeks with 4-6 patients per group and therapists/yoga instructors.

1. STUDY OBJECTIVES

1.1. Primary Objective

Our primary aim is to examine the short-term and long-term treatment efficacy of yoga (physical exercises/postures, meditation/mindfulness, and breathing exercises) for treating Generalized Anxiety Disorder (GAD) as compared to conventional CBT for GAD and to a stress education (SE) control condition. This study would provide the first RCT data for the comparative efficacy and acceptability of a standardized yoga group for the treatment of GAD compared to an active control, as well as gold standard CBT for GAD, and would generate a strong evidence base to support clinical use and future research.

Specific Aim 1: Short-term Efficacy of Yoga: Our primary objective is to examine the short-term treatment efficacy of yoga on GAD symptoms. We expect that, at post-treatment, a significantly greater proportion of individuals randomized to receive yoga will be classified as “responders” to treatment (CGI-I ≤ 2) than for individuals who receive SE (Hypothesis 1.1). We further expect that a greater proportion of individuals receiving CBT for GAD will be classified as “responders” than for those receiving SE (Hypothesis 1.2). Moreover, we predict that the rate of “responders” in individuals receiving yoga will be comparable to those receiving CBT at post-treatment (Hypothesis 1.3).
Specific Aim 2: Long-term Efficacy of Yoga: Our secondary aim is to examine the long-term treatment efficacy of yoga on GAD symptoms. We hypothesize that yoga and CBT will be equally effective at the 6-month follow-up (i.e., the “responder” rate for yoga will not be inferior to that for CBT), and that yoga and CBT will each have higher “responder” rates than SE (Hypothesis 2.1-2.3).

1.2. Secondary Objectives

Specific Aim 3: Mediation Analyses. Our tertiary aim is to examine and compare the mechanism of treatment changes in yoga and traditional CBT for GAD. We predict that treatment changes in

responder rates during yoga treatment will be mediated via changes in mindfulness and changes in vagal tone (Hypothesis 3.1), whereas changes in CBT will be mediated via changes in maladaptive cognitions (Hypothesis 3.2.). Moderators of "responder rates" will also be examined.

2. BACKGROUND AND RATIONALE

2.1. Background on Condition, Disease, or Other Primary Study Focus

The lifetime prevalence rate of generalized anxiety disorder (GAD) is estimated to be 5.7% [1] and is associated with high comorbidity, suffering, and burden. Traditional cognitive behavior therapy (CBT) is the gold-standard intervention for treating anxiety disorders [2], including GAD (e.g., [3]). Individuals with GAD show lower levels of mindfulness (e.g., [4]), and therapy that enhances mindfulness appears to be effective for GAD (e.g., [5]). However, few individuals suffering from these symptoms receive adequate treatments because CBT in general, let alone mindfulness-based CBT is still not widely disseminated. Some yoga practices share many similarities to this intervention. In fact, meditation is a core component of most yoga practices, both historically and in practice. This notion is consistent with the NCCAM definition of yoga: "Yoga in its full form combines physical postures, breathing exercises, meditation, and a distinct philosophy." (http://nccam.nih.gov/health/yoga/introduction.htm).

In contrast to mindfulness-based CBT, yoga has been widely adopted, more readily available and its popularity is increasing. Surveys suggest that 10% of the U.S. population have tried yoga or meditation [6], and 20 million more Americans want to [7]. Yoga has been adopted by the advertising industry as a symbol of health and a wholesome lifestyle. A recent survey of complementary and alternative medicine (CAM) use by the NIH and the Centers for Disease Control revealed that in 2007, 6.1% of the population had tried yoga as a therapeutic intervention and that yoga and its component practices of deep breathing and meditation were in the top 10 of the most prevalent CAM practices and among 4 that showed the greatest increase in the previous 5 years [8]. A recent survey by Dr. Khalsa indicated that stress was one of the largest reasons (73%) for yoga participation [9]. The lack of evidence base for GAD is surprising, given that yoga practices are potentially powerful emotion regulation techniques with reductions in self-reported anxiety reported in both healthy subjects [10-12] and psychiatric inpatients [13]. Furthermore, a brain imaging study revealed that GABA neurotransmitter levels were elevated immediately after a single yoga class, and after 12 weeks, were associated with improvements in mood and anxiety in healthy subjects [14, 15]. Reductions in anxiety have also been reported after yoga programs applied over weeks or months in normal populations [16-18], students under exam stress [19], stressed caregivers [20], and otherwise healthy subjects with self-reported chronic distress [21, 22]. Preliminary studies by Dr. Khalsa- one of the co-investigators- have shown that yoga has been effective in reducing anxiety in musicians [23, 24], high school students, and GAD patients (see Preliminary Data). In summary, yoga is a frequently used, easily accessible, and a popular form of mind-body medicine that includes meditation practices. Previous studies suggest that yoga is an effective anxiety-reduction method. However, no systematic investigation has been conducted to provide an evidence base, critical for clinical

recommendations and reimbursement as well as treatment optimization for the efficacy of yoga for GAD.

2.2. Study Rationale

Yoga is an established and traditional practice that emphasizes mindful awareness. Mindfulness-based strategies can significantly enhance treatment of GAD. Our recent meta-analytic review of 39 studies of mindfulness-based strategies in a variety of populations revealed effect sizes of 0.97 for improving anxiety symptoms in patients with a mix of anxiety disorders, including GAD [25]. Patients are taught to respond to stressful situations more reflectively rather than reflexively, thereby countering experiential avoidance strategies. Through the sustained regular practices of yoga that include elements of mindfulness/meditation/mind-body awareness, there are ultimately long-term changes that take place in perception and interpretation of both internal (thoughts) and external (environmental) events, leading to reduced frequency and intensity of stress/anxiety responses. The physical postures and the regulation of breathing in yoga repetitively lead to reduced stress activation with resulting decreases in sympathetic and hypothalamic pituitary axis activity. Through a feedback loop, possibly through the vagal system, this physiological down-regulation may further enhance the effect of meditation and yoga to reduce perceived stress/anxiety. These strategies are also effective for targeting worrying, a future-oriented maladaptive cognitive process predominant in GAD (e.g., [25-27]). In general, exercises that encourage acceptance, mindfulness and present-moment experiences may be particularly promising strategies to counter worrying [5, 28, 29]. Yoga practice in its traditional multicomponent and contemplative-focused form should thus be particularly beneficial for GAD. This widely used practice is a comprehensive system of exercises for physical and psychological health and well-being, and incorporates multiple techniques including physical postures/exercises, breathing exercises, relaxation strategies, and meditation/concentration techniques. Basic research on yoga and its component techniques demonstrate reductions in arousal, and improved mood states and health [30-39]. Clinical yoga research studies [40] have demonstrated improvements in anxiety in patients with a variety of medical conditions including cancer [41-44], migraine [45], irritable bowel syndrome [46, 47], depression [48, 49], and others [50].

A review of controlled studies of yoga for anxiety problems identified 8 studies [19, 49, 51-56], but the quality of these studies precludes definitive conclusions [57, 58]; some studies, including our own [59] demonstrated reductions in test anxiety [49, 59] and obsessive compulsive disorder [51]. Five uncontrolled (single group) published studies show improvements in anxiety symptoms with yoga with mixed psychopathology [60-62] or primarily anxiety disorders populations [63, 64], and controlled but non-randomized studies in anxiety disorders in India [52, 56]. To date, only 6 randomized controlled trials were published, and of these, 5 evaluated anxiety in mixed populations with depression or other problems [53, 54, 65-67]. Thus, existing studies on yoga for anxiety have been of low quality with small sample sizes, and few with random assignment. Most importantly, these studies have focused on a variety of anxiety-related conditions but with widely varied entry criteria. Although these studies convey an overall impression of potential efficacy for GAD, critically, only one of these studies evaluated a population with DSM-IV entry criteria for GAD, and this study was primarily a breathing intervention [68]. The proposed study is, therefore, entirely novel in this rigorous and necessary approach to evaluating yoga efficacy for GAD; rigorous RCT data is needed before Yoga can be adapted as an approved intervention by insurers and clinicians, as well as to allow

future examination of effective yoga elements in future evidence based interventions or to target specific subpopulations for whom yoga may be most effective. Should yoga, which is a popular practice, be found effective for GAD, these results could have a significant public health impact as yoga could be considered by primary care doctors as a first line treatment option improving public health access to effective GAD interventions, including potentially reducing medication use, such as benzodiazepines, in primary care with its inherent risk for abuse and dependence.

To control for attention from instructors, expectancy effects, and group support effects, Stress Education (SE) will be employed as an active control intervention. SE is currently used in NIH-funded protocols at the Benson-Henry Institute for Mind-Body Medicine at MGH (see Letter). Participants will be provided with detailed and extensive information about stress and health, but will not receive any CBT, yoga, or other mind-body training techniques. Content areas will include definitions of stress and the stress response, the fight or flight response, physiological and psychological effects of stress, stress and performance, the negative stress cycle, stress and health/illness, stress and immunity, stress buffers, stress hardiness, stress and heart disease, the role of genes and environment in health, the contribution of lifestyle behaviors such as caffeine and alcohol intake and cigarette smoking, and the importance of regular exercise and proper diet (without specific instructions for exercise or dietary changes). For the daily home practice subjects will listen to SE audio CDs containing information about nutrition and positive perspectives on lifestyle and emotions (see Research Design).

Examining yoga as a strategy for treating GAD is highly innovative, both from a clinical and theoretical perspective, and would generate a strong evidence base to support clinical use as well as future research. This study would provide the first RCT data for the comparative efficacy and acceptability of a standardized yoga intervention for the treatment of GAD compared to an active control as well as the gold standard CBT for GAD. Yoga is widely available and popular while there is a paucity of trained CBT therapists and many individuals will not seek professional help. Should the yoga intervention be found to have efficacy for GAD, future research using dismantling component designs could examine the relative efficacy of the specific components of yoga practice (physical exercises, breath regulation, meditation, relaxation). For example, an intervention primarily consisting of breath regulation in the absence of the other components might provide information on the contribution of this technique to efficacy of the whole practice. Such information could then be used to refine the yoga intervention or allow development of hybrid, augmentation of other evidence based treatment approaches. Although this study will employ a standardized yoga intervention from a specific yoga style, it is likely that less standardized yoga practices, including other styles of yoga, in their traditional multicomponent format that are generally available to the public would also have efficacy, and this could also be evaluated experimentally in future studies. Initial data about the impact of Yoga in stress related biomarkers in GAD would further help guide future research examining potential biological mechanisms underlying response to Yoga in GAD. For example, future studies could examine the biological impact of yoga on anxiety neurocircuitry using neuroimaging. Finally, Yoga could be compared to first line pharmacotherapy for GAD in future studies. Other innovative aspects include the following:

(1) Clinical innovation. Although CBT is effective, few GAD patients receive adequate CBT, primarily because CBT is still not widely disseminated. In contrast, yoga is widely practiced. Although practices that encourage mindfulness may help alleviate anxiety, including GAD (e.g., [25]). Although early data on the efficacy of yoga for GAD are promising [77], very

little systematic research has been conducted. Results of this proposed study would have important clinical implications that could have immediate applicability for clinical recommendations about yoga.

(2) Theoretical innovation. Worrying in GAD is a maladaptive, future-oriented, cognitive process (e.g., [26, 78]). Certain aspects of yoga may target worrying in GAD by enhancing mindfulness and present-moment awareness (e.g., [5]) as opposed to emphasizing maladaptive cognitive beliefs about worrying (meta-cognitions) and its consequences (e.g., [79, 80]). Directly comparing CBT and yoga for GAD would, therefore, answer important theoretical questions about the mechanism of treatment change. These results may also influence the nosology of the disorder, which has been a controversial issue for the DSM-V.

CBT for GAD ([2], Journal of Clinical Psychiatry). We conducted a meta-analysis of randomized clinical trials that randomly assigned adults with an anxiety disorder to CBT or placebo. Of 1,165 studies, 27 met all inclusion criteria. Across all the anxiety disorders, random effect models of completer samples yielded a pooled effect size (Hedges' g) of 0.73 (95% confidence interval, 0.88-1.65) for continuous anxiety severity and a pooled odds ratio of 4.06, demonstrating CBT for GAD was moderately effective (Hedges' g = 0.51, 95% CI: 0.05-0.97). Similar results were reported by Mitte [81], with an average placebo-controlled effect size of 0.57. The pre-post effect size for reducing anxiety was 0.82.

Mindfulness-based interventions for GAD [25]We conducted a meta-analysis of 39 studies of mindfulness-based treatments for anxiety symptoms in anxiety and depression that did not include CBT strategies specifically targeting maladaptive cognitions, and found an effect size (Hedges' g) of 0.81 (95% CI: 0.35-1.27, z=3.47, p<.01), suggesting mindfulness-based strategies are potentially beneficial for GAD.

Yoga improves stress, resilience, anxiety and affect in students [82, 83]. We have shown that yoga yields mental health benefit in two separate semester-long randomized controlled trials. For students randomly assigned to 12 weeks of regular physical education or yoga classes, yoga resulted in significantly better outcomes on the Perceived Stress Scale (PSS; [84]) ($p<0.05$) and the Resilience Scale. Further, yoga may also have been protective against worsening on anxiety and test anxiety subscales of the BASC-2, the tension/anxiety subscale of the Profile of Mood States (POMS-SF) and mindfulness, as measured by the Child Acceptance and Mindfulness Measure (CAMM: see Figure). The slight deterioration seen in the control group has been previously recorded in high school settings and is consistent with the high levels of mental health problems in adolescents. These data suggest a protective/preventive effect of yoga on stress, resilience, anxiety and mindfulness.

Yoga improves anxiety, affect and mindfulness [23, 24, 85]. In a series of studies, musicians in summer fellowship programs at the Tanglewood Music Center were recruited to a 6-week yoga program (~3 classes/week). Our first study demonstrated significantly greater improvements over time in solo performance anxiety on the Performance Anxiety Questionnaire (PAQ) and the POMS tension/anxiety subscale (t-test $p<0.05$) (see figure; all figures have yoga=filled bar, controls= open bar) and a trend to significance on the POMS total ($p=0.08$, not shown).

In a second study, the yoga intervention showed a significant reduction in PAQ ($p=0.011$) and the POMS tension subscale ($p=0.038$) (not shown). Of note, Five Facet Mindfulness Questionnaire (FFMQ) scores and subscales of "observing" and "awareness" were significantly

greater in the yoga group ($p<0.05$). In a controlled study of yoga (n=31) compared to no treatment (n=25) for performance anxiety in adolescent musicians. The yoga group (filled bars in figure) showed a decrease from 48.9 (±17.8 SD) to 41.4 (±15.4 SD) ($p<.001$) on the Music Performance Anxiety Inventory – Adolescents (MPAI-A) with little change in the control group (open bars); $p>0.4$. In another, more recent study, Drs. Khalsa and Hofmann co-advised a doctoral dissertation [59] to evaluate the effectiveness of a 9-week yoga practice on reducing music performance anxiety in undergraduate and graduate music conservatory students, including both vocalists and instrumentalists. The intervention consisted of 14 60-minute yoga classes approximately twice a week and a brief daily home practice. Of the 24 students enrolled in the study, 17 attended the post-intervention assessment. Participants who completed the measures at both pre- and post-intervention assessments showed large decreases in music performance anxiety as well as in trait anxiety as measures with the STAI ($d = 1.05$). Improvements were sustained at 7- to 14-month follow-up.

The yoga practices of the proposed study improve anxiety symptoms in GAD patients [77] For effect size estimates for the proposed study, we conducted a pilot trial on the efficacy of the planned yoga intervention in 16 participants with GAD. The majority of the sample was female (87.81%) and Caucasian with an average age of 50 (SD: 11.46, range: 31-70). The most common comorbid diagnosis was major depressive disorder (18.75%).

Similar to earlier trials examining mindfulness-based treatments for GAD (e.g., [86]), we administered the Symptom Check List (SCL-90-R, [87]). In addition to paired t-tests (all 2-tailed), we estimated the effect size using Cohen's d: $[M_{post}-M_{pre}]/SD_{pre}$. Significant reductions from baseline to endpoint were observed in the anxiety subscale, $t(15) = 4.88$, $p < .0001$, $d = .86$, the depression subscale, $t(15) = 4.98$, $p < .0001$, $d = .96$, and the global severity subscale, $t(15) = 4.58$, $p < .0001$, $d = .76$. In this intervention, daily assigned home practice was recommended but not rigorously monitored; at midpoint only 10% of respondents reported no home practice, whereas 40% of respondents practiced with a 30-50% compliance level, suggesting even greater compliance can be achieved with specific emphasis and monitoring as will occur in the proposed trial. Overall, although no control group was included, these pilot data support the feasibility and potential efficacy of yoga for GAD as will be more rigorously examined in the proposed randomized study compared to standard CBT for GAD and a stress education control.

Reason for choosing 12-weekly training: There has been no standard duration established for yoga treatment protocols (Sherman, 2012). However, there is certainly ample precedent for yoga research trials with 12-week treatment duration. For example, there are published yoga research trials with 12-week interventions for conditions including back pain (Sherman et al., 2011; Tilbrook et al., 2011; Herman et al., 2005), stress-related symptoms and diagnoses (Kohn et al., 2013), cancer (Speed-Andrews et al., 2010; Bower et al., 2011, 2012; Moadel et al., 2007; McDonald et al., 2006), epilepsy (Rajesh et al., 2006), incarceration (Harner et al., 2010) hemodialysis (Yurtkuran et al. , 2007), respiratory disorders (Santana et al., 2013), dementia (Fan eta al., 2011), falling/balance in the elderly (Schmid et al., 2010), prediabetes (Yang et al., 2011; Benavides et al.,2009), binge eating (McIver et al., 2009), and in healthy subjects (Streeter et al., 2010; Phoosuwan et al., 2009; Cohen et al., 2009). There is currently little research information on the week-by-week or even month-by-month timecourse of improvements in outcomes in yoga trials (i.e. duration response curves) because few longitudinal studies with multiple assay time points have been conducted. In two yoga research trials with back pain with

primary outcomes measured at mid-treatment and at end-treatment at 12 weeks, there were progressive increases in improvements [Sherman et al. 2005, 2011]. Similarly in a study of yoga for COPD, 24 class-by-class measures of pain and distress throughout a 12-week yoga intervention showed steady and apparently linear improvements over time (Donesky-Cuenco et al., 2009). The co-investigator on this grant (Khalsa) has conducted a yoga intervention for chronic insomnia in which measures of insomnia every 2 weeks revealed that improvements increased incrementally over the 8 weeks of the intervention with the strongest improvements at the beginning of the intervention (Khalsa, 2004, 2009). Finally, most relevant to our proposed trial, was a 12-week yoga intervention in incarcerated women, in which anxiety levels showed a similar consistent improvement from baseline through weeks 4, 8 and end-treatment at 12 weeks, again with the largest improvements near the beginning of the intervention but still with some improvements continuing near the end (Harner et al., 2010). Moreover, given that the standard CBT interventions for GAD in our clinic and laboratory are 12 weeks long, it is important for the research design to have all 3 treatment arms of the same duration. Otherwise, we may face the potential criticism that differences in outcome between the different treatment arms could be due to differences in treatment duration rather than to the content of the therapy itself. Different treatment durations would involve differences in subject investment, time and effort, and in therapist interaction time; all of these are nonspecific confounding factors which would compromise the interpretation of the primary research goal to evaluate the difference in efficacy of the therapies themselves, i.e. yoga vs. CBT vs. inactive control.

Reason for examining biomarkers of response with cortisol and a marker of cardiac vagal tone: The underlying pathological cognitive process of GAD is worrying, which is an anticipatory process attempting to prevent or minimize future problems and may act as a cognitive avoidance strategy to reduce negative emotions associated with intrusive catastrophic images (Borkovec et al., 1998). Worrying has been associated with reduced autonomic flexibility as a result of low cardiac vagal tone in numerous studies (Borkovec& Hu, 1990; Hoehn-Saric& McLeod, 2000; Hofmann, Moscovitch, Litz, Kim, Davis, &Pizzagalli, 2005; Hofmann, Schulz, Heering, Muench, &Bufka, 2010; Lyonfields, Borkovec, & Thayer, 1995; Thayer, Friedman, &Borkovec, 1996).

We will measure cardiac vagal tone by recording respiratory sinus arrhythmia (RSA). RSA refers to the rhythmic variations in heart rate that occur at the frequency of respiration, and reflects parasympathetic control over the heart (e.g., Berntson, Cacioppo, & Quigley, 1993). To measure breathing, a flexible respiration band will be strapped around subjects' chest. A software program computes RSA using the peak-valley method (Grossman, 1983). This method derives RSA by calculating the difference between the minimum interbeat interval during inspiration and the maximum interbeat interval during expiration.

Assessment of cortisol and RSA will allow complementary assessment of biomarkers of response to the three interventions. These biomarkers will allow brief, inexpensive and standardized assessments that may suggest potential pathways for efficacy of yoga compared to the CBT and control conditions for GAD.

3. STUDY DESIGN

The purpose of the proposed study is to determine whether yoga is an effective method for treating GAD, and its relative efficacy compared to a standard psychosocial intervention. For

this purpose, we will conduct a randomized controlled trial. Using superiority tests, yoga (N = 95) will be compared to SE (N = 40), a commonly used control condition. Using non-inferiority tests, yoga will compared to standard CBT for GAD (N = 95). To improve comparisons, all interventions will be conducted in a group format over 12 weekly sessions with 4-6 patients per group and therapists/yoga instructors. We anticipate having approximately 3 yoga instructors, 3 CBT therapists, and 3 SE instructors, along with 2 IEs per enrolling site. All interventions will be conducted at anxiety out-patient clinics in Boston (the Center for Anxiety and Related Disorders at Boston University and the Center for Anxiety and Traumatic Stress Disorders at Massachusetts General Hospital). The third study site, NYU Langone Medical Center in New York City, will not recruit participants and will conduct data analysis and interpretation as well as study oversight. Subjects in all 3 treatment groups will be provided with a credible rationale for the efficacy of their assigned treatment. At each study treatment visit, patients will complete various psychological measures. Some of the study visits require more in-depth assessments involving saliva sample collection, meeting with a study doctor, and a physical examination (see the section 6.1 for more information). The four independent evaluator blinded assessments occur pre-treatment (baseline visit), mid-treatment (Week 6), post-treatment (Week 12), and at a six-month follow-up.

The Clinician Global Impression-Severity Scale (CGI-S) and Improvement Scale (CGI-I) [93] will be used in determining remission and response criteria. Treatment response is defined as a CGI-I of 1 (very much improved) or 2 (much improved). Remission is defined as CGI-S of 1 (not at all ill) or 2 (borderline ill). Treatment response will be the primary outcome measure. This allows for a direct comparison with other studies because CGI is the gold-standard measure across clinical trials. Our research team has decades of experience using the CGI, which has excellent psychometric properties and is treatment sensitive [94-97]. Bandelow et al. [94] analyzed clinical trials with more than 5,000 patients with GAD, social anxiety, and depression; the CGI is highly correlated with anxiety and depression scales across disorders.

Trained study clinicians blind to randomized treatment assignment (independent evaluators, IEs) will administer diagnostic assessments and rating scales. All raters will be clinicians who will have undergone specific training to criterion in the use of the study measures (See Integrity of Assessment Procedures in 6.1). To assess for DSM psychiatric diagnoses, study approved independent evaluators (IEs) will use the standard diagnostic intake interviews at each site. These are the Structured Clinical Interviews for DSM-IV and DSM-5 (anticipated to be available in line with enrollment) at MGH and the Anxiety Disorders Interview Schedule (ADIS-5 [92]) at BU. GAD and other diagnostic criteria are identical in the instruments, and DSM-5 is unchanged from DSM-IV for GAD. Each principal investigator has extensive experience with diagnostic interviews, and all raters will be cross certified (see section 6.1 for rater certification and reliability procedures and for assessment details). All clinician rated assessments will be administered by certified blind Independent Evaluators (IEs)

Based on our current study experience, we expect that we will need to screen as potentially eligible twice the number of patients ultimately consenting and that 90% of patients consented will be ultimately enter the randomized phase of treatment after they received a study diagnostic assessment. We conservatively estimate that 20% of eligible participants will discontinue the intervention prematurely, but all participants who are randomized will be included in the analysis with an intent to treat analytic approach. For ethical reasons, additional

treatment will not be withheld for non responders (defined as CGI-I > 2) or anyone for whom additional intervention is indicated in any intervention condition during the 6 month follow up. Non responders (CGI-I>2) at week 12 will be assisted in finding appropriate care from our existing referral resources. All participants will receive 6 month assessments, but any additional treatment received by non responders will be adjusted for in the analyses.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 and 4.2 Inclusion and Exclusion Criteria.

All study candidates must meet inclusion criteria and those meeting any of the exclusion criteria below will not be entered into the randomized trial.

Table 1 below lists all inclusion and exclusion criteria.

Table 1: Inclusion and Exclusion Criteria and Rationale.

Inclusion Criteria	***Rationale***
Male or female outpatients 18 years of age or older with a primary psychiatric diagnosis of generalized anxiety disorder	Population under study
CGI-severity score of 4 or higher	Adequate pre-treatment severity
Off concurrent psychotropic medication for at least 2 weeks prior to initiation of randomized treatment, OR stable on current medication for a minimum of 6 weeks and willing to maintain a stable dose	Treatment confound
Willingness and ability to perform the yoga intervention and to comply with the requirements of the study protocol.	Human subjects concerns
Exclusion Criteria	
Patients unable to understand study procedures and participate in the informed consent process.	Human subjects concern
For women of childbearing age: Pregnant (based on urine pregnancy test), planning to become pregnant, or lack the use of approved methods of birth control	Human Subjects Safety
Serious medical illness or instability for which hospitalization may be likely within the next year	Feasibility, subject safety
Significant current suicidal ideation or suicidal behaviors within the past 6 months	Subject safety
History of head trauma causing loss of consciousness, or seizure disorder resulting in ongoing cognitive impairment	Treatment confound, subject safety
Posttraumatic stress disorder, substance use disorder, eating disorder, or organic mental disorder within the past 6 months	Treatment confound
Lifetime history of psychotic disorder, bipolar disorder, or developmental disorder	Treatment confound
Significant personality dysfunction likely to interfere with study participation (assessed during the clinical interview)	Treatment confound
Prior experience with (more than 5 Yoga classes or CBT sessions within the last 3 years) and/or current practice of mind-body techniques (e.g., yoga, meditation, Tai-Chi, etc) or CBT	Treatment confound
Concomitant psychotherapy for GAD (any psychotherapy)	Treatment confound
Physical conditions that might cause injury from yoga (pregnancy, physical injuries and musculoskeletal problems)	Human subjects concern and subject safety

Cognitive impairment (MOCA≤21)	Human subjects concern and safety

Equitable Selection of Subjects:
The study population is representative of the population with a primary diagnosis of GAD that stands to benefit from this research. All participants will be adults capable of providing informed consent. We are not excluding any participants based on race, ethnicity, or gender. Participants are selected on the basis of their diagnostic status. Because the use of yoga has not been rigorously tested in pregnant women, those women who are pregnant or not using a reliable form of birth control are excluded from the study. Because the treatment approaches that will be used in this study have never been tested in individuals younger than 18 and might need to be adapted for younger children, children under 18 are excluded from this study. Children between the ages of 18 and 21 will be included. Because a full understanding of the group sessions (yoga, CBT, or SE) is necessary for treatment and sessions will be conducted in English, subjects who are not fluent in English will be excluded from participation.

4.3. Study Enrollment Procedures

SUBJECT RECRUITMENT

Recruitment methods:
Participants will be recruited from patients who present for treatment, are referred or are directly recruited through IRB approved advertisement at the Center for Anxiety and Related Disorders at Boston University (CARD) and the Center for Anxiety and Traumatic Stress Disorders (CATSD) at Massachusetts General Hospital (MGH). Types of recruitment strategies will include advertisements in the media, postings online, particular email services, and clinical referrals.

At MGH, we will be posting information on our own program websites. At MGH, mails and letters will be sent out with a description of our study through the MGH All-User Broadcast and the RSVP for Health program. We will run advertisements in local publications, such as the Metro. We will use the IRB approved CATSD re-contact log (at MGH), Participants who have agreed to be re-contacted in the future will receive emails, letters, and/or phone calls.

Similarly, we will additionally recruit participants for the BU site through postings on our web site, BU's quickie-jobs, and flyers posted at public locations, such as cafes, bookstores, supermarkets, etc. We will further use the IRB approved CARD re-contact log, Participants who have agreed to be re-contacted in the future will receive emails, letters, and/or phone calls.

These recruitment strategies are all aimed at reaching a diverse population.

Individuals who contact our centers will be screened initially by phone for interest in the proposed research, as well as general diagnostic and study eligibility, and interest in research participation. Data for participants who undergo the phone screening process will be de-identified and recorded in the study database phone screening log. Reasons for ineligibility and for non-participation of eligible subjects will be recorded.

Consent and eligibility for randomization procedure:

Interested patients who are eligible for participation will be scheduled for an evaluation meeting where informed consent will be obtained. All potential participants will review the consent form, risks, and benefits associated with the protocol with an approved study investigator and will sign consent prior to completion of any study assessments in this protocol.
The study investigator will explain the study, answer any questions, and obtain written informed consent. Participants will be given as much time as needed to review the consent and ask questions prior to participation in study procedures. The study procedures and consent form will be approved by the Institutional Review Board at each of the participating sites prior to study initiation.

Potential participants will undergo formal structured clinical interviews and rating scales (see Assessment section 6.2 for detail) to confirm diagnosis and eligibility. Patients will then undergo safety assessments including medical history, medication use, and laboratory tests, including urine toxicology screen and pregnancy test (for women of childbearing age). In addition, our MD or nurse with MD oversight familiar with the yoga intervention will determine whether the participant is fit for yoga and CBT based on a baseline medical history and physical exam to determine whether study exclusion criteria are met, and any identified medical concerns will be reviewed with signed permission with participant's PCP prior to study entry.
We expect to screen and consent approximately 295 individuals such that 230 will meet eligibility criteria and agree to be randomized across the 2 sites.

Randomization Procedure

After eligibility criteria are determined and participants have completed a baseline assessment, and confirmed availability to participate, participants will be randomly assigned to either Yoga, CBT, or stress education (SE) using the variable-sized permuted block randomization procedure (stratified by site).

Our study statisticians will set up the randomization table stratified by site and with variable-sized permuted blocks (maximum block size will be 6 to minimize cohort effects). The variable-sized permuted block randomization schedules will be generated by Dr. Rosenfield (the supervising biostatistician) prior to enrolling the first subject into the study. Randomization will be stratified by site, and groups of 4-6 individuals will be randomized at a time to one of the 3 treatment conditions. Randomizations will be conducted in SAS using the procedures outlined by Efird (2011) [Efird, J. Blocked Randomization with Randomly Selected Block Sizes. *Int. J. Environ. Res. Public Health., 8, 15-20.].* The randomization code will be emailed by Ms Keshaviah (the trial statistician) to the study coordinator only when the randomization occurs, i.e. once the last participant of each group has completed baseline.

5. STUDY INTERVENTIONS

5.1. Interventions, Administration, and Duration

We propose to administer the treatment in a group format to better reflect the most commonly available yoga format, and to maximize feasibility and cost-effectiveness (see also Integrity of Treatment Procedures). Providing all 3 modalities in the same sized and length group format will also maximize integrity for the comparison of the active treatment components. All three treatments will be 2 hours in duration, allowing for 15 minutes of study logistics including

discussion of subject questions or difficulties with the home or group interventions, evaluation of individual subject compliance, and strategizing enhancing compliance. The treatment itself will comprise a full 105 minutes training and practice in each group session. Subjects in all 3 treatment groups will be provided with a credible rationale for the efficacy of their assigned treatment. Subjects in the CBT arm will be informed of the role of CBT in the efficacy of changing dysfunctional thought patterns and beliefs, subjects in the yoga arm will be informed of the role of yoga in changing cognitive and physical emotional and stress reactivity through the postures, breath regulation and meditation components of yoga practice, and subjects in the stress education control will be informed of the role of stress education in understanding the psychophysiological basis of stress and anxiety as a basis for overcoming stress and anxiety.

CBT: The 12 session CBT treatment will be based on the standardized protocol developed at one of our centers (CARD) and widely available [88]. An earlier version of this protocol has been empirically supported in individual and group settings [89]. This protocol is comprised of four primary treatment modules including cognitive restructuring, progressive muscle relaxation, worry exposures, and in vivo exposure exercises. See Appendix reference for CBT for GAD manual. The protocol describes session-by-session a 12-session CBT treatment. The initial sessions describe the cognitive behavioral model of worry and GAD. Each session consists of a different "lesson." These lessons initially cover basic information about the nature of the anxiety and worry, the possible function and negative consequences of worrying, the maladaptive and paradoxical effects of attempting to control and suppress one's thoughts, the basic cognitive errors of probability overestimation and catastrophic thinking, adaptive strategies to deal with worries, such as problem solving, worry exposure, which may involve exploring and exposing the patient to negative images and scenarios that might be behind some of the worrisome thoughts (e.g., a person who worries losing his or her job might be exposed to the image of sitting under the bridge as an abandoned lonely homeless person). Subjects will also be assigned to complete approximately 20 minutes of homework daily, which will be recorded in a homework log. In addition, our treatment protocol will target meta-cognitions (i.e., worrying about worrying). To target meta-cognitions, we will use treatment recommendations from Wells (2009). More specifically, the primary content of the sessions are as follows:

Session 1. Discussing the basic structure of the treatment program and logistics. Discussing commonalities among group members. The nature of generalized anxiety disorder and worry; outlining of treatment procedures and basic principles underlying treatment.
Session 2. The function of anxiety: When is it adaptive when not? Learning to recognize maladaptive anxiety.
Session 3: The purpose and function of anxiety.
Session 4: A closer look at generalized anxiety disorder.
Session 5: Basic relaxation strategies (12-step progressive muscle relaxation).
Session 6: Thoughts that cause anxiety I: Probability overestimation.
Session 7: Thoughts that cause anxiety II: Catastrophic thinking (thinking the worst).
Session 8: Thoughts that cause anxiety III: Worrying about worrying.
Session 9: From worry exposure to worry prevention.

Session 10: Dealing with real problems (problem solving strategies).
Session 11: Identifying obstacles in the future.
Session 12: Accomplishments and future plans.

Yoga: The yoga intervention will apply Kundalini Yoga practices as taught by Yogi Bhajan. This is a well-known, accessible style of practice in the U.S. that incorporates all of the traditional components of yoga including physical postures and exercises, breathing techniques, relaxation exercises and meditation practices. It is a safe style of yoga that is registered with the Yoga Alliance that is readily and routinely adapted for therapeutic purposes. The 12-week yoga intervention will consist of 12 group classes and assigned daily home practice led by qualified and certified yoga instructors. Each group yoga session will include physical postures/exercises, breathing techniques, meditation and deep relaxation practice that are all easy to learn and do not require extensive practice or athletic ability to perform. Subjects' current physical health, flexibility and endurance will be screened at study entry. The yoga instructor will again review all preexisting conditions with subjects in the group at the beginning of the 12-week intervention and will make modifications to the practices as necessary to ensure subject safety and to prevent injury. The instructor will also require subjects to report any recent changes in their health, injuries or conditions at the beginning of every treatment session. Group size will be relatively small for yoga classes with 4-6 subjects per group, which allows for careful monitoring of subject safety during the class sessions.

Audio CD's will be provided to guide subjects through daily home practices throughout the 12-week intervention to achieve mastery and self-efficacy. The 20-minute session will begin with spinal flexibility and loosening for a physical release of tension and increased body awareness. Subjects will then practice a breathing meditation specifically recommended for coping with anxiety. In general yoga and meditation home practice compliance is reported as being feasible and equivalent to that of other behavioral interventions [74, 90, 91]. Dr. Khalsa, a co-investigator on this study, has observed compliance in a home yoga intervention averaging 29 minutes of a daily assigned 45-minute intervention (unpublished data). We believe that we will observe adequate compliance from the proposed home intervention, and with more rigorous follow-up to encourage adherence, and expect better compliance than in our pilot trial (see preliminary data above.)

Stress Education Group (SE): SE will also include 12 weeks of group and home practice sessions. SE will control for attention from instructors, expectancy effects, and group support effects, Stress Education (SE) will be employed as an active control intervention. SE is currently used in NIH-funded protocols at the *Benson-Henry Institute for Mind-Body Medicine* at MGH. In this condition, participants will be provided with detailed and extensive information about stress and health, but will not receive any CBT, yoga, or other mind-body training techniques. Content areas will include definitions of stress and the stress response, the fight or flight response, physiological and psychological effects of stress, stress and performance, the negative stress cycle, stress and health/illness, stress and immunity, stress buffers, stress hardiness, stress and heart disease, the role of genes and environment in health, the contribution of lifestyle behaviors such as caffeine and alcohol intake and cigarette smoking, and the importance of regular exercise and proper diet (without specific instructions for exercise or dietary changes). For the daily 20 minute home practice subjects will listen to SE audio CDs containing information about nutrition and positive perspectives on lifestyle and emotions. Therefore, we believe that comparable social and attention controls will be placed in the SE group.

5.2. Handling of Study Interventions (Treatment Integrity)

Treatment Certification and Supervision Procedures

The senior therapists who lead the CBT and yoga groups will have at least 1 year of practice in the treatment modality. Yoga instructors will have undergone a formal 200-hr yoga teacher training program, and be registered with the Yoga Alliance. CBT instructors will be clinical psychologists trained in CBT for GAD. In addition, all therapists will undergo trainings in the specific study intervention: in CBT by Dr. Hofmann, in yoga by Dr. Khalsa and SE overseen by Dr. Hoge. Dr. Khalsa has extensive expertise in both yoga, as a certified yoga instructor with over 40 years of yoga practice and instruction, and in yoga research design, as a full-time yoga researcher for over 10 years and a leading yoga research consultant and collaborator internationally. Therapists in the stress education control treatment will have been trained by the Benson Henry Institute for Mind Body Medicine stress education control intervention currently in use in ongoing studies. The training format and level for CBT and yoga will be similar to the training of therapists conducted at the Beck institute (Dr. Hofmann has been trained as a therapist and supervisor of CBT by the Beck Institute of Cognitive Therapy). The training will include a 3-day workshop with ongoing supervision of cases. The training procedures will consist of didactic instruction and hour-for-hour supervision of one or two concurrent training cases. Therapists-in-training will attend supervision meetings, at which both specific application and general issues of the CBT and yoga treatments will be discussed. Therapists will continue to receive weekly supervision from Drs. Hofmann, Khalsa and Hoge, respectively, for the duration of the study, and variations in the protocol will be addressed during this weekly supervision. In the event that a therapist does not adhere to the treatment protocol or displays behavior of questionable competence, this study therapist may be asked to undergo additional training procedures before continuing as a study therapist.

Treatment Fidelity

Treatment integrity will be further insured through careful supervision and adherence monitoring of all three interventions. A random 20% of the recorded sessions of each intervention will be reviewed and fidelity ratings completed to provide feedback to the therapists/instructors using standardized adherence forms including required and prohibited elements for each intervention to prevent drift. All therapists will also complete a detailed and systematic log/report of each completed treatment session which will be reviewed in supervision along with Working Alliance Inventory.

5.3 Concomitant Interventions

Subjects will be instructed not to initiate any psychotropic medications or additional psychological interventions during the course of the study. Subjects may receive prescription medications not specifically excluded by the protocol (e.g., aspirin, cold preparations, oral contraceptives, and vitamins). Patients have to be off concurrent psychotropic medication for at least 2 weeks prior to initiation of randomized treatment, or stable on current medication for a minimum of 6 weeks and willing to maintain a stable dose. All concomitant medication will be closely assessed and monitored in the study.

5.3.1 Allowed Interventions

See 5.3.

5.3.2 Required Interventions

None

5.3.3 Prohibited Interventions

1) Prior experience with Yoga and/or CBT (more than 5 Yoga classes or CBT sessions within the last 3 years)
2) Current practice of mind-body techniques (e.g., yoga, meditation, Tai-Chi, etc) or CBT
3) Also prohibited is any concomitant psychotherapy for GAD.
4) Initiation of anxiolytic pharmacotherapy during the 12 session treatment period is not allowed (see 8.0 exception under Intervention Discontinuation)

5.4 Adherence Assessment

Monthly reports will monitor subject enrollment, completion, attrition, and individual subject progress as well as the completion of critical assessments. Additional reports will be done as needed to monitor baseline characteristics, protocol adherence, and other issues of interest.

Treatment integrity will be insured through careful supervision and adherence monitoring of all three interventions (see above Treatment Fidelity).Patient adherence will be measured by session attendance, and the Homework Compliance Scale. The working alliance inventory will also be assessed. Based on the available data, non-adherence to CBT, yoga, and SE instructions are unlikely to be of great concern. In fact, patients are likely to be highly motivated to practice strategies that may result in immediate relief of their suffering without experiencing any unpleasant side effects. Nevertheless, patient adherence will be considered as a moderator in the final analysis. Binary adherence will be defined as for use in the per protocol analysis as attending at least 10 of the 12 group treatment sessions in addition to a score of at least 4 on the homework compliance scale (higher than moderate compliance of 3) out of a scale of 0-6.

6. STUDY PROCEDURES

6.1. Schedule of Evaluations

Form Type	Measure	Admin By	Mo. -1 (Screen*)	Wk 0 (Baseline)	Wks 1-5	Wk 6 (Mid Tx)	Wks 7-11	Wk 12-13 (Post Tx)	Wk 36-37 (6 mo. FU)
Diagnosis & Screening	Eligibility/Informed Consent	IE + RA pre-screen	X						
	SCID/ADIS-5	IE	X						
	CGI-S/CGI-I[1, 2]	IE	X	X	X (biweekly)	X	X (biweekly)	X	X
	SIGH-A	IE	X	X		X		X	X
	Demographics	Self	X						
	Medical History	MD/RN	X						
	Screening Medications/Therapy Log	MD/RN	X						
	Physical Exam	MD/RN	X						
	MoCA	MD/RN	X						
Secondary Outcomes	STAI	Self		X		X		X	X
	BAI	Self		X	X (biweekly)	X	X (biweekly)	X	X
	BDI-II	Self	X	X		X		X	X
	PSS	Self		X		X		X	X
	WHOQOL-BREF	Self		X		X		X	X
	SCL-90	Self		X		X		X	X
	PSWQ	Self		X	X (weekly if in CBT)	X	X (weekly if in CBT	X	X
	ISI	Self		X				X	
	PSQI	Self		X				X	
	SOCI	Self						X	
	ASQ	Self		X		X		X	X
Mediators	MCQ	Self		X		X		X	X
	FFMQ	Self		X		X		X	X
Psycho-physiological & Biological stress	ECG (RSA)	RA		X		X		X	X
	Salivette Sample	Self		X		X		X	X
	Affect Grid	RA		X		X		X	X
	Vital Signs	RA		X		X		X	X
Tx Details	Credibility / Expectancy	Self		X		X		X	X
	Homework compliance	Self			X (weekly)	X	X (weekly)	X	
Safety & Integrity	Adverse Events Log[3]	RA		X	X (weekly)	X	X (weekly)	X	X

	Concomitant Medications/Therapy Log[3]	RA		X	X (weekly)	X	X (weekly)	X	X
	Suicidality checklist[2]	IE	X	X	X (biweekly)	X	X (biweekly)	X	X
	Working alliance	Self				X		X	
	SAFETY Form	RA		X	X (weekly)	X	X (weekly)	X	X
	End of Study	RA	Completed after 6-month FU/early termination visit						
	Protocol Deviations	RA	Ad hoc, as needed						
Quality Assurance	Adherence/ Competence	Fidelity rater	20% of sessions (per schedule sent by study statistician)						
	Inter-rater Reliability	IE	15% of sessions (per schedule sent by study statistician)						

*Data collected during the screening is part of routine clinical care; Wk=Week; Mo=Month; FU=Follow-up; Tx=Treatment; IE=Independent Evaluator; MD/RN=Physician/Nurse; [1]The CGI-I will not be administered at the screening or baseline, as it captures post-baseline improvement; [2]Administered weekly if the CGI-I≥5 at any time; [3]Information gathered by the RA will be reviewed by the therapist/instructor prior to each weekly class.

6.2 Description of Evaluations

Assessment Instruments and Procedures

All clinician-rated outcomes will be assessed by Independent Evaluators (IEs) blind to treatment assignment. The IEs will be M.D., Ph.D., or experienced Masters-level diagnosticians with previous research experience with structured interviewing who will receive additional training and certification for this study under the direction of Drs. Simon and Hofmann with certification by Dr. Eric Bui. Any new raters will undergo training including rating at least 2 audio or videotaped interviews then have 2 interviews taped and reviewed for agreement by an expert rater. In addition to the training procedures, study staff will 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 should also reduce the potential for interviewer drift. A two-level system will be used to maintain the reliability of diagnoses and of other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected clinical assessments, which will all be digitally recorded. Each month, an independent evaluator (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 us 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.

Interview-Based Measures

Structured Diagnostic Interview (SCID): The Structured Clinical Interview for DSM-IV (SCID-IV: will be updated to SCID5 as soon as available, anticipated prior to enrollment) will be

administered at MGH CATSD to determine the absence of diagnostic exclusion criteria and assess co-occurring psychiatric disorders.

The Anxiety Disorders Interview Schedule for DSM-5 (ADIS-5; [92]) will be used at BU to determine DSM-5 psychiatric diagnoses (please note that the ADIS-5 was developed at the Center for Anxiety and Related Disorders at Boston University, therefore, this interview is already available to us).

Each principal investigator has extensive experience with diagnostic interviews, and all raters will be certified. Cross site certifications and quality assurance ratings will occur to assure rating consistency of diagnoses as administered in the SCID with the ADIS, an overlapping interview.

Clinical Global Impression of Severity (CGI-S; [94-97]): This is a 1-item scale asking the investigator to assess the patient's overall level of illness severity. The clinician should integrate all aspects of the patient's condition when using this scale. It will be used at assessments.

Clinical Global Impression of Improvement (CGI-I; [93]): This 1-item instrument allows evaluators to give an overall rating to subject's level of improvement or worsening on a scale of 1-7, with 1 correlating to very much improved and 7 correlating to very much worse. It will be used at assessments.

Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; [98])This 19-item structured, clinician-administered rating scale provides an overall measure of anxiety. It will be used at assessments.

Self-Report Measures

Demographics Form: Patients will be asked to fill out a questionnaire regarding age, race, ethnicity, gender, socioeconomic status in addition to their religious beliefs and practices.

State-Trait Anxiety Inventory (STAI; [100]): The STAI-A is a 40-item, multiple-choice questionnaire that differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." As a result, it is useful in both clinical and research contexts. It will be used at assessments.

Beck Anxiety Inventory (BAI; [101]): This 21-item self-report inventory designed to measure severity of anxiety symptoms in psychiatric populations has high internal consistency and test-retest reliability. It will be used at assessments.

Beck Depression Inventory (BDI-II; [102]): This 21-item self-report inventory designed to measure severity of depression symptoms in psychiatric populations has high internal consistency and test-retest reliability. It will be used at assessments.

Perceived Stress Scale (PSS; [84]): This 10-item scale is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. It will be used at assessments.

Symptom Checklist 90 (SCL-90; [87]): This is a 90-item instrument used to assess to what degree certain problems and complaints bothered or distressed an individual during the past week. It will be used at assessments.

Quality of Life Scale (WHOQOL-BREF; [103]): This instrument assesses quality of life enjoyment and satisfaction. It will be used at assessments.

Meta-cognition Questionnaire (MCQ; [106]): This is a 65-item instrument used to assess beliefs people have about their thinking. It will be used at assessments.

Five-Facet Mindfulness Questionnaire (FFMQ; [104,105]): This scale has recently been developed to measure trait-like aspects of six sub-factors: observing/noticing experience; acting with awareness, avoiding "auto pilot"; describing/labeling; non-judging of self-experience; non-reacting to internal experience; kindness/compassion/friendliness. The factor structure of this scale has been validated. It will be used at assessments.

Penn State Worry Questionnaire-Past Week (PSWQ-PW; [107]): This is a 15-item, self-report measure of worry (PSWQ) Items are rated on a five-point Likert scale, and are summed to form a total score ranging from 16 to 80. The PSWQ has excellent psychometric properties in student, community, and clinical samples. It will be used at assessments.

Pittsburgh Sleep Quality Index (PSQI; [140]): This is a 19-item, self report measure of sleep quality over a one month duration. The items make up seven different component scores consisting of sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. This measure also generates a global sleep quality score. It will be used at assessments.

Insomnia Severity Index (ISI; [141]): This is a 7-item, self-report measure to assess insomnia as defined by the DSM-IV. It will be used at assessments.

Affective Style Questionnaire (ASQ; [142]): This is a 20-item, self report measure to assess individual differences in emotion regulation.

Social Identification Scale (SOCI; [143]): A 11-item, self report measure to assess social identification with the treatment group in order to determine if social identification is a potential confounder or effect modifier for our primary and secondary outcomes.

Psychophysiological/Biological Measures of Stress

Endocrinological Stress Measure (Cortisol). Following the methodology by Vreeburg et al. [108], we will measure the salivary cortisol awakening response at each assessment point. Subjects will collect saliva samples using Salivettes (Sarstedt) at home on a regular working day

representative of their regular sleep/wake schedule at 4 time points (at habitual wake time and at 30, 45 and 60 minutes later) and will return the samples to the investigators. Cortisol analysis will be performed by competitive electrochemiluminescence immunoassay using standard procedures; the functional detection limit is 2.0 nmol/L and the intra and inter-assay variability coefficients in the measuring range are <10%. All 4morning salivary cortisol values will be used to calculate the area under the curve as a measure of the dynamic of the cortisol awakening response, which will be evaluated before and after the three treatments. Cortisol analyses will include covariates for smoking status and oral contraceptive use.

We will measure cardiac vagal tone by recording respiratory sinus arrhythmia (RSA). RSA refers to the rhythmic variations in heart rate that occur at the frequency of respiration, and reflects parasympathetic control over the heart (e.g., Berntson, Cacioppo, & Quigley, 1993). To measure breathing, a flexible respiration band will be strapped around subjects' chest. A software program computes RSA using the peak-valley method (Grossman, 1983). This method derives RSA by calculating the difference between the minimum interbeat interval during inspiration and the maximum interbeat interval during expiration. [127-134].

Treatment Moderator Measure

Credibility/Expectancy Questionnaire: This questionnaire is used to examine whether credibility and expectancy moderates therapy outcome.

Study Integrity and Safety Measures

Montreal Cognitive Assessment (MoCA; [113]):This is a 10-item rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. This measure will be used to assess entry criteria.

Homework Compliance Scale[110, 111]: This is a 1-item clinician-rated instrument. It assesses homework compliance and will be administered prior to each session.

Working Alliance Inventory (Short Form; [112]): This is a 12-item self-report instrument. It assesses the working alliance and will be administered prior to each session.

Adverse Events Monitoring Form: Adverse events will be assessed at each visit. Adverse events will be rated as mild (noted change in the subject's condition that causes minor distress and does not affect activity), moderate (notable distress and/or mild disruption in usual activity), or severe (marked distress and/or major disruption in usual activity).

Concomitant Medications: *Concomitant medication* is defined as any medication taken on or after the start of double-blind investigational product. Concomitant drug use will be summarized by the number and proportion of patients in each treatment group receiving each drug within each therapeutic class. Multiple drug use by a patient will be counted only once.

Medical Review Form: A study nurse with MD oversight or physician will assess physical fitness with the medical history form and a standard physical exam, emphasizing musculoskeletal, neurologic, and cardiac history. Participants' current health status, medical history, past surgeries, and past psychiatric medication use will be assessed. Pregnancy will be assessed by a urine pregnancy test at the screen for women of childbearing age.

6.2.1. Screening Evaluation.

Individuals who contact the Center will be screened initially by phone for interest in the proposed research, as well as general diagnostic and study eligibility, and interest in research participation. Data for participants who undergo the phone screening process will be de-identified and recorded in the study database phone screening log. Reasons for ineligibility and for non-participation of eligible subjects will be recorded.

Interested patients who are eligible for participation will be scheduled for an evaluation meeting where informed consent will be obtained.

Consent: The consent process will be conducted by an experienced member of the study and staff. All potential participants will review the consent form, risks, and benefits associated with the protocol with an approved study investigator and will sign consent prior to completion of any study assessments in this protocol. The study investigator will explain the study, answer any questions, and obtain written informed consent. Participants will be given as much time as needed to review the consent and ask questions prior to participation in study procedures. The study procedures and consent form will be approved by the Institutional Review Board at each of the enrolling sites prior to study initiation. There will be a single informed consent form at each enrolling site that describes both the assessment and study procedures.

We will allow a maximum of one month for the time between baseline assessment of participants and randomization. For any participant for whom completing the screening process is delayed, with PI approval baseline measures will be repeated prior to entry. Once participants complete eligibility and are randomized to a group, they will start treatment within 4 weeks.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Participants will be enrolled in the study once they sign the informed consent form. Enrollment will be tracked in the study enrollment log.

Baseline Assessments

For participants who have successfully been screened for eligibility and are enrolled into the study, baseline assessments are performed against which to measure the study outcome. A complete list of the baseline evaluations are presented in Table 6.1.

Randomization

Randomization will precede the intervention.

We will allow a maximum of one month for the time between baseline assessment of

participants and randomization; should more than one month pass for logistical reasons, baseline assessments would be repeated prior to randomization. Once participants complete eligibility and are randomized to a group, they will start treatment within 4 weeks.

6.2.3 Blinding

Independent evaluators will remain blind to treatment assignment throughout the study. To preserve the blind they will be instructed with a reminder script for patients not to discuss their treatment prior to an assessment. The randomization codes will be created by the study statistician prior to entry of the first patient in the trial. Randomization will be stratified only by site. No unblinded analyses will be performed prior to study completion, unless specifically requested by the DSMB, in which case study PIs will only see blinded safety comparisons of the study intervention groups.

The trainers/therapists and the person handling the randomization code cannot be blinded, but they will not be involved in IE ratings, which will be used for outcomes in this trial. The PIs will supervise the treatments, and oversee all study participants including safety and adverse events. The PIs will not, however, know the subject's patient codes and the PIs will not be involved in the independent evaluator ratings. Thus these clinical and oversight study staff will not have access to data and have no influence on the outcome data. Outcome ratings will be completed by the blinded independent evaluators. The data management and analysis will be completed by the study statisticians and data manager who are not involved in clinical treatment or safety assessment at any time.

6.2.4 Follow-up Visits

At mid-treatment visit (week 6 after enrollment), post-treatment assessment (Week 12-13) and 6-month follow-up (Week 36-27):

- *Clinical improvement (CGI-I)*
- *Self-report instruments (STAI, BDI-II, BAI, PSS, SCL-90, WHOQOL-BREF, MCQ, FFMQ, PSWQ, ISI, PSQI, ASQ)*
- *Psychophysiological/biological measures of stress (RSA, cortisol)*
- *Measures of study integrity and safety (Adverse Events, Concomitant Medications/Therapy log. homework compliance, working alliance)*

6.2.5 Completion/Final Evaluation

See 6.2.4.

6.3 Visit Windows

If a subject cannot complete a study given visit within the windows specified below, all efforts should be made to have the subject's visit occur as close to the window as possible.

Any visits that occur out of window should be noted by the RA in the REDCap Protocol Deviation (PROTDEV) Log project.

Screening / Baseline

- ≤4 weeks should elapse between a subject's screening and baseline assessment.
- If a subject's baseline visit cannot be scheduled within 4 weeks of their initial screening visit (e.g., because their cohort does not fill up due to slow accrual), then they will need to be re-screened. At the re-screening visit, all Screening measures should be repeated, and the subject's SCID/ADIS GAD diagnosis should be confirmed.

Baseline / Treatment

- ≤4 weeks should elapse between a subject's baseline assessment and treatment initiation.

IE Assessments

- A window of +/- 7 days will be used for biweekly IE assessments
- A window of -30/+60 days will be used for the 6-month follow-up visit
- Week 6 and week 12 IE assessment should only occur after the week 6 and week 12 (i.e. final) treatment sessions (CBT, yoga, or SE), respectively.

Treatment Sessions

- No visit windows will be used for weekly group treatment sessions.

7. SAFETY ASSESSMENTS

For reasons of patient safety, patients who do not respond to SE after the 12 week intervention will be given the choice to receive CBT or yoga. Specifically, non responders (CGI-I >2) will be assisted in finding appropriate care from our existing referral resources. Additional treatments will be monitored and considered in the analyses. Subjects who wish to discontinue their participation at any point will also receive referral assistance if they request additional treatment.

Patients will be excluded if they report significant current suicidal ideation (as assessed with the BDI-II item 9 and CSS suicidality checklist) or suicidal behaviors within the past year. We will also exclude patients with seizures disorder resulting in ongoing cognitive impairment, patients with a history of head trauma causing loss of consciousness, seizures or ongoing cognitive impairment, patients with medical illnesses or instability for which hospitalization may be likely within the next year, and patients with physical conditions that might cause injury from yoga (e.g., physical injuries, musculoskeletal problems).

7.1 Specification of Safety Parameters

A study MD or nurse with MD oversight will assess medical history and with consent will consult with PCPs if any medical issues that may potentially interfere with safe participation in yoga are identified. We have modified our study criteria to more clearly exclude all potential subjects with physical disabilities (evaluated with a medical history and physical exam) or cognitive disabilities (evaluated by the Montreal Cognitive Assessment Scale) that would clearly preclude safe practice of the yoga intervention or CBT. At present there is insufficient information regarding the safety of yoga during pregnancy. For reasons of safety, all women of childbearing potential will be required to use a reliable form of birth control throughout the

study: (e.g.: oral contraceptives, surgical sterilization (of the subject or of her male partner), IUD (intrauterine device), condom and spermicide or diaphragm and spermicide). Subjects with existing or planned pregnancy during the intervention will be excluded. Inclusion of subjects with any minor preexisting conditions of potential concern will be subject to participation only after consented review with and approval by the subject's primary healthcare provider.

Each visit, adverse events will be assessed on the adverse events monitoring form and rated as mild, moderate, or severe (as defined in AE section below). On weeks 0, 2, 4, 8, 10 and 12 the CGI-S, CGI-I, BDI and a suicidality checklist will be administered to evaluate any potential worsening symptoms. Physical fitness will be assessed by the study nurse with MD oversight or MD with the medical history form and a standard physical exam, emphasizing musculoskeletal, neurologic and cardiac history.

Twenty-four-hour emergency coverage with a study clinician (physician, psychologist or registered nurse with MD oversight) will be available. Patients will be provided with cards with the emergency contact number. In the event of an emergency the clinician will determine the necessary clinical intervention and will provide and coordinate appropriate care.

Parameters

All three interventions (Yoga, CBT, and SE) are safe interventions with minimal associated risk.

We anticipate minimal risk to subjects due to their participation in this study; however, some risks are associated with conducting these treatments. The primary risk is the evocation of uncomfortable levels of anxiety or other emotions during some treatment sessions. Some patients may find sessions stressful and react to them with anxiety. However, it is not expected that anxiety will be higher than what they would experience in other life situations. Participants will be informed about these risks and told that they may withdraw from the study at any time and may refuse to complete any treatment procedures they find too uncomfortable.
Some patients may feel uncomfortable about the treatment sessions being taped (necessary for supervision and treatment adherence checks). However, this will be a required procedure. The purpose of the taping will be explained, confidentiality will be maintained, and informed consent for taping will be obtained. Additionally, clients may experience some disruption of daily activities due to scheduling of treatment sessions.

There is a possibility that a patient may become distressed when being asked about symptoms or personal experiences during the diagnostic evaluation or assessment sessions. The primary risks to the patient are discomfort associated with the assessments and the treatment procedures. Subjects may also experience some discomfort or anxiety from discussing personal information. Yet, this anxiety is not expected to be any greater than that subjects already experience, and subjects will be able to withdraw from the study at any time. There are risks of injury during yoga. The practice of the physical exercises and postures, breathing exercises, relaxation techniques, and meditation in the yoga treatment involve little risk, although at times subjects may find them challenging and difficult to complete. Overexertion on the physical exercises may lead to temporary muscle soreness for up to a week. However, subjects will be instructed to gradually increase their effort on the physical exercises and breathing practices so as not to overexert themselves, and to stop if any subjects experience unexpected unpleasant symptoms. There may be risks and side effects that are currently unknown and/or unanticipated.

Study personnel will be monitoring the patients' clinical and physical conditions carefully and will withdraw patients from the study if warranted by their clinical condition. The yoga instructor will again review all preexisting conditions with subjects in the group at the beginning of the 12-week intervention and will make modifications to the practices as necessary to ensure subject safety and to prevent injury. The instructor will also require subjects to report any recent changes in their health, injuries or conditions at the beginning of every treatment session. Group size will be relatively small for yoga classes with 4-6 subjects per group, which allows for careful monitoring of subject safety during the class sessions.

In addition to the risks associated with the treatments, interviews, and questionnaires, there are some other potential risks from the electrocardiograms, such as an allergic reaction to the electrode paste. However, these reactions are rare and typically very mild.

Although every effort will be made to assure confidentiality, it is possible someone could without permission gain access to study related data during the time they are being used or stored for examination of results.

7.3 Adverse Events and Serious Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) are defined as follows.

An **adverse event (AE)** is defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen.

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

These events will be assessed at each visit using the adverse events monitoring form and rated as mild, moderate, or severe. These parameters are defined as follows: mild (noted change in the subject's condition that causes minor distress and does not affect activity); moderate (notable distress and or mild disruption in usual activity); and severe (marked distress and/or major disruption in usual activity).

7.4 Reporting Procedures

Unexpected, serious, and intervention-related SAEs will be reported to the NYU, BU and MGH IRBs, DSMB, and NCCAM, in accordance with requirements. Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCAM Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCAM Program Officer within 15 days. Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the DSMB, IRB, NCCAM, and other oversight organizations in accordance with their requirements.

7.5 Follow-up for Adverse Events

We will first administer the SAFTEY form at each visit. This form asks if any AE's have occurred. If the subject answers "yes" we will then fill out the cumulative AE LOG accordingly.

Adverse events will be assessed at each visit using the adverse events monitoring form and rated as mild, moderate, or severe. These parameters are defined as follows: mild (noted change in the subject's condition that causes minor distress and does not affect activity); moderate (notable distress and or mild disruption in usual activity); and severe (marked distress and/or major disruption in usual activity).

7.6 Safety Monitoring

This study will be overseen by a study DSMB and associated DSMP, as well as the IRB at each study site. Additional monitoring by NCCAM may occur.

2. Frequency of Data Review for this Study— The frequency of data review for this study differs according to the type of data and can be summarized in the following table:

Data type	Frequency of review	Reviewer
Summary figure of subject accrual & summary table of reasons for exclusion (based on protocol enrollment criteria)	PIs weekly for first three months of recruitment, then weekly accrual and quarterly adherence; DSMB yearly	PI, DSMB
Summary table of status of all randomized subjects, as of date of reporting	PIs monthly, DSMB yearly	PI, DSMB
Summary tables of adherence to IE visits and treatment sessions	PIs quarterly, DSMB yearly	PI, DSMB
Summary table of demographic characteristics of all randomized subjects	PIs monthly, DSMB yearly	PI, DSMB
Summary tables of all (serious) adverse events	PIs quarterly, DSMB yearly	PI, DSMB
Detailed descriptions of SAEs	Per Occurrence	PI, DSMB, IRB, NCCAM
Full study continuing review	Yearly	IRB (MGH, BU, and NYU respectively)

8. INTERVENTION DISCONTINUATION

8.1 Treatment Discontinuation and Monitoring:

Any participant with a CGI-I of 5 or greater at any time will undergo weekly assessment by a study clinician including clinical and safety assessments, CGI-S and CGI-I ratings and suicidality assessment (CSS suicidality checklist) Participants will be discontinued from study participation at their request at any time or if warranted in the clinical judgment of the study clinicians. Additionally, participants who score >5 on the Clinical Global Impression of Improvement Scale for 2 consecutive weeks (much worse) or who develop suicidality at any point will be discontinued from the treatment protocol and referred for clinically appropriate care. In these instances, the subject will be evaluated by a study clinician and a decision will be made regarding possible exit from the study and/or referral for treatment. We will report all episodes of worsening symptoms and the outcome of the attendant monitoring procedure to our DSMB.

In addition, if the BDI-II suicidality item (item number nine) is above 1 (scale is from 0 to 3) or the CSS suicide checklist is above 2, a study clinician will assess the patient weekly to determine suicidality and if present, assist with accessing any indicated clinical intervention. This assessment will occur weekly until the BDI-II item is no longer above a 1 and CSS suicidality item is no longer above 2.

Twenty-four-hour emergency coverage with a study clinician (physician, psychologist, or registered nurse with MD oversight) will be available. Patients will be provided with cards with the emergency contact number. In the event of an emergency the clinician will determine the necessary clinical intervention and will provide and coordinate appropriate care.

All participants will be encouraged to complete a final endpoint assessment unless clinically inappropriate even if they discontinue treatment, and all analyses will be intent to treat. Every effort will be made to keep appropriate subjects in the study for the full duration of the trial. Subjects dropping out of the trial will be included in data analysis as described in the Data Analysis Section.

Non responders (CGI-I >2) will be assisted in finding appropriate care from our existing referral resources. Additional treatments will be monitored and considered in the analyses. Furthermore, subjects who wish to discontinue their participation at any point will also receive referral assistance if they request additional treatment.

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.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The specific aims and hypotheses are as follows:

Specific Aim 1: Short-term Efficacy of Yoga: Our primary objective is to examine the short-term treatment efficacy of yoga on GAD symptoms. We expect that, at post-treatment, a significantly greater proportion of individuals randomized to receive yoga will be classified as "responders" to treatment (CGI-I ≤ 2) than for individuals who receive SE (Hypothesis 1.1). We further expect that a greater proportion of individuals receiving CBT for GAD will be classified as "responders" than for those receiving SE (Hypothesis 1.2). Moreover, we predict that the rate of "responders" in individuals receiving yoga will be comparable to those receiving CBT at post-treatment (Hypothesis 1.3).
Specific Aim 2: Long-term Efficacy of Yoga (Exploratory Aim): Our secondary aim is to examine the long-term treatment efficacy of yoga on GAD symptoms. We hypothesize that yoga and CBT will be equally effective at the 6-month follow-up (i.e., the "responder" rate for yoga will not be inferior to that for CBT), and that yoga and CBT will each have higher "responder" rates than SE (Hypothesis 2.1-2.3).
Specific Aim 3: Mediation Analyses. Our tertiary aim is to examine and compare the mechanism of treatment changes in yoga and traditional CBT for GAD. We predict that treatment changes in responder rates during yoga treatment will be mediated via changes in mindfulness and changes in vagal tone (Hypothesis 3.1), whereas changes in CBT will be mediated via changes in maladaptive cognitions (Hypothesis 3.2.). Moderators of "responder rates" will also be examined.

These hypotheses can be tested in a five-year multi-site study to examine the comparative efficacy of yoga, CBT, and stress education, a previously employed control condition, for patients with GAD. Patients with GAD will receive 12-weekly yoga, CBT, or stress education sessions delivered in a group format controlling for attention, time, and group format. Independent evaluators will perform assessments before the 12-session intervention phase, at mid-treatment, after the intervention, and at 6-month follow-up.

9.2 Sample Size and Randomization

A non-inferiority test is the most direct test of our hypothesis that Yoga will be as effective as CBT for both short-term and long-term outcomes. We will perform a non-inferiority test using response rate (response rate is defined as CGI-I ≤ 2) as the outcome on which to compare CBT and Yoga at post-treatment and at follow-up. Since some attrition may occur, we will use last observation carried forward to insure an intent-to-treat analysis. The non-inferiority margin will be half the difference in response rates between the active comparison (CBT) and placebo. Based on earlier literature, we can expect response rates in our particular CBT and placebo conditions of 57.9% in CBT and 22.2% in placebo. Thus, our non-inferiority margin will be set at ½ the difference between 56.7 and 22.2, or 17.85%. Using the power analysis program PASS 12, we find that the number of subjects required to obtain .80 power for the non-inferiority test comparing CBT and Yoga is 95 participants in each of the 2 conditions. We verified this number in a 1000 simulation Monte Carlo study using these same parameters. This number is higher than the number proposed in the original grant. Thus, we will increase the N per cell in CBT and Yoga to 95 (22 additional patients per site) to have adequate power for this non-inferiority test. While the original study was budgeted based on a lower number of participants, with careful management of costs we believe we can manage this increase in participants within the full study budget if awarded as proposed.

For the superiority tests (CBT vs. SE and Yoga vs. SE) on the secondary outcomes (which are continuous), we used the MRM power analysis program PinT 2.12. We assumed 25% missing data, and used data from our recent CBT trials (e.g., Stern et al., 2012) to estimate the variances and covariances needed for PinT. PinT indicated greater than .80 power to detect an effect size as small as d=.27, between a small (d=.20) and medium (d=.50) effect size.

We predict that changes in mindfulness will mediate changes in outcome over time for patients in the Yoga condition, and changes in cognitions will mediate changes in CBT. Plus, changes in RSA and cortisol may also mediate changes in outcome across conditions. We further predict that treatment condition will moderate the effect of Time on the mediators ("a" paths).

We performed a Monte Carlo study to calculate the power for our proposed bootstrap mediation analysis. Based on our recent trial, we assumed that the "a" paths (the effects Yoga vs. SE and of CBT vs. SE on the mediators) would be large, and that the relation between each mediator and the outcome (response to treatment) would have a medium effect size. The Monte Carlo study consisted of 400 samples, for each of which we performed a bootstrap mediation analysis, each consisting of 1,000 resamples for the bootstrap analysis. Results showed a power greater than .81 to detect a mediated pathway.

Treatment Assignment Procedures

Please see Randomization procedures section 4.3.

Independent evaluators will remain blind to treatment assignment throughout the study. To preserve the blind they will be instructed with a reminder script for patients not to discuss their treatment prior to an assessment. The randomization codes will be created by the study statistician prior to entry of the first patient in the trial. Randomization will be stratified only by site. No unblinded analyses will be performed prior to study completion, unless specifically requested by the DSMB, in which case study PIs will only see blinded safety comparisons of the study intervention groups.

9.3 Definition of Populations

Our primary analyses will use mixed-effects regression models (MRMs) with a logistic linking function (a GLMM analysis) since our primary outcome measure is dichotomous (treatment response). Analyses of secondary outcomes will be performed using MRM. MRM and GLMM easily accommodate nesting of repeated observations within subjects, include all who complete at least one assessment (including the baseline assessment), and are the preferred method to analyze longitudinal data (Hamer and Simpson, 2009 [135]). Our intent-to-treat sample includes all randomized patients who complete at least one assessment. Thus, our primary analyses (GLMM and MRM) are intent-to-treat analyses. We will also perform "per protocol" analyses. Our per protocol population will include all randomized patients who complete the baseline and post-treatment assessments, miss no more than 2 treatment sessions, who average a 4 or higher on the homework compliance scale, and who did not initiate prohibited treatment during the study. We will repeat our GLMM and MRM analyses using the per protocol sample.

9.4 Interim Analyses and Study Stopping Rules

No interim analyses are planned, unless requested by the DSMB or NCCAM. DSMB reports for safety will be prepared yearly (see DSMP) without unblinded treatment outcomes analyses unless specifically requested by the DSMB. Unexpected, serious, and intervention-related SAEs will be reported to the NYU, BU, and MGH IRBs, DSMB, and NCCAM, in accordance with requirements. In addition, all study treatment discontinuations for clinical worsening will be reported to the DSMB. 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.

9.5 Outcomes

As noted earlier, a non-inferiority test is the most direct test of our hypothesis that Yoga will be as effective as CBT for both short-term and long-term outcomes. We will perform a non-inferiority test using response rate (response rate is defined as CGI-I ≤ 2) as the outcome on which to compare CBT and Yoga at post-treatment and at follow-up. Since some attrition may occur, we will use last observation carried forward to insure an intent-to-treat analysis. The non-inferiority margin will be half the difference in response rates between the active comparison (CBT) and placebo. Based on earlier literature, we can expect response rates in our particular CBT and placebo conditions of 57.9% in CBT and 22.2% in placebo. Thus, our non-inferiority margin will be set at ½ the difference between 56.7 and 22.2, or 17.85%. Using the power analysis program PASS 12, we find that the number of subjects required to obtain .80 power for the non-inferiority test comparing CBT and Yoga is 95 participants in each of the 2 conditions. We verified this number in a 1000 simulation Monte Carlo study using these same parameters. This number is higher than the number proposed in the original grant. Thus, we will increase the N per cell in CBT and Yoga to 95 (22 additional patients per site) to have adequate power for this non-inferiority test. While the original study was budgeted based on a lower number of participants, with careful management of costs we believe we can manage this increase in participants within the full study budget if awarded as proposed.

For the superiority tests (CBT vs. SE and Yoga vs. SE) on the secondary outcomes (which are continuous), we used the MRM power analysis program PinT 2.12. We assumed 25% missing data, and used data from our recent CBT trials (e.g., Stern et al., 2012) to estimate the variances and covariances needed for PinT. PinT indicated greater than .80 power to detect an effect size as small as d=.27, between a small (d=.20) and medium (d=.50) effect size.

9.5.1 Primary Outcome

Response (CGI-I of 1 or 2) will serve as the primary outcome measure alongside the SIGH-A as the core secondary continuous measure.

9.5.2 Secondary Outcomes

Secondary Outcomes: Secondary outcome measures include the STAI, PSS, BDI-II and BAI, WHOQOL-BREF, PSQI, ISI, ASQ, and PSWQ. The FFMQ, MCQ, RSA, and cortisol are examined as possible mediators of change.

The Credibility/Expectancy Questionnaire will be administered to examine whether credibility and expectancy moderates therapy outcome.

In addition, we will explore whether clinical characteristics (comorbid diagnoses) and demographic characteristics (age, sex, SES) are possible moderators. The data analyses are described for the primary measure only.

9.6 Data Analyses

Primary Analyses

Our primary analyses will use mixed-effects regression models (MRMs) with a logistic linking function (a GLMM analysis) since our primary outcome measure (response to treatment, defined as CGI-I≤2) is dichotomous. Analyses of secondary outcomes will be performed using MRM. MRM and GLMM easily accommodate nesting of repeated observations within subjects, include all subjects with at least one assessment, and are the preferred method to analyze longitudinal data (Hamer and Simpson, 2009 [135]). Since these analyses will include all subjects who are randomized and complete at least one assessment, it is an intent-to-treat analysis. Also, since subjects will undergo treatment in groups (4-6 subjects per group) our MRM and GLMM models will include 3 levels: repeated measurements (level 1) nested within subjects (level 2) who will be nested within their treatment cohort (level 3).

Our primary model will be a GLMM in which response to treatment over time will be modeled as a growth curve. Our primary analyses will examine outcomes at post-treatment (Aim 1). These analyses will include only the 7 assessments from baseline to post-treatment, and will not include the follow-up (FU) assessment since it could be affected by subjects seeking other treatments during the FU period. Only our exploratory analyses for outcome at FU (Aim 2) will include data from the FU assessment. Since recent research indicates that suboptimal modeling of the growth curve can result in incorrect results, we will examine various linear and nonlinear models to find the optimal growth curve during treatment (linear, quadratic, cubic, exponential [leveling off at an asymptote], and an ANOVA model, in which time is coded as a categorical variable. For this ANOVA model, each assessment time point is modeled with a dummy coded assessment variable [coded 1 for the assessment, 0 for other assessments]. In this model, the means at each assessment point are freely estimated and are not constrained to fit any particular pattern. See our discussion of the ANOVA model in the paragraph below for more information).We will conduct our significance tests using the growth curve that most accurately models the data (comparing the various growth curve models using AIC and BIC).

The three treatment conditions (Yoga, CBT, and SE) will be coded using 2 dummy variable contrasts, with SE as the "reference" treatment. The first dummy variable will contrast Yoga vs. SE, and the second will contrast CBT to SE. Time will be coded as weeks since baseline. To test of differences between treatments at post-treatment (week 12), time will be centered at week 12 (in other words, our Time variable in our analysis will be computed as "time minus 12"). In MRM or GLMM analyses in which this Time centered variable is used, the significance of the dummy variable contrasts (Yoga vs. SE and CBT vs. SE) provides the test of the differences between these treatment conditions at post-treatment. A similar approach can be used to test differences between treatment conditions at follow-up.

This growth curve model will be used to test differences between treatment conditions for our primary outcome (response to treatment) and for CGI-S, since these outcomes are measured frequently enough (7 times during treatment) to accurately model the growth curve. However, the other secondary outcomes are measured at most3 times during treatment (baseline, week 6, post-treatment), with secondary sleep measures administered only twice (baseline and post-treatment), thus disallowing accurate assessment of their growth curve. Thus, these outcomes will use an MRM employing an ANOVA type design (see for example, Liu, Rovine, &

Molenaar, 2012). In this kind of model, time is treated as a categorical variable (using2 dummy variables [one for each assessment except the baseline assessment] to code the 3 assessments). The three treatment conditions (Yoga, CBT, and SE) will be coded using the 2 dummy variable contrasts (Yoga vs. SE and CBT vs. SE). Interactions will be formed between each treatment condition contrast and each assessment dummy variable. This coding freely estimates the means for the outcome at each assessment, without any constraint from a specific growth curve. This design is similar to a 3 x 3 repeated measures ANOVA with the exception that it includes all patients that complete at least one assessment, the outcome can be dichotomous, the covariance structure of the repeated measures can take almost any form, and this approach assumes data are missing at random (MAR) or not missing completely at random (MCAR). The significance of the interaction between a treatment condition contrast (e.g., Yoga vs. SE) and an assessment dummy variable (e.g., for the post-treatment assessment) will test whether the change from baseline to that assessment is significantly different between the treatment conditions. Using this coding scheme, all contrasts between treatment conditions at all assessments are provided by this one analysis. Thus, this approach has the added benefit of having all contrasts between the treatment conditions at each assessment being conducted on the same sample.

Demographics and comorbid diagnoses will be used as covariates in all analyses and considered as possible moderators of outcome at each assessment. An additional moderator that will be investigated is homework adherence.

Planned Secondary Analysis of Sensitivity of Growth Curve Model for Primary Outcome

To determine if the results of the analyses for Aim 1 are sensitive to the growth curve model, we will perform a secondary analysis, using a simple ANCOVA-type model, to verify the results of our primary growth curve model. Since the outcome is binary (response to treatment), this analysis will be performed using logistic regression, with the following predictors of outcome at post-treatment: baseline severity based on the CGI-S and SIGH-A, and the two dummy variables coding the contrast between SE and the 2 active treatments. This analysis will be performed twice: once as an ITT analysis with missing outcomes imputed as last observation carried forward, and once as a completer analysis.

Per Protocol Secondary Analysis:

As additional secondary analyses, we will repeat our GLMM and MRM analyses using the per protocol sample. We will use these analyses rather than simpler analyses (such as logistic regression or repeated measures ANOVA) because repeating our GLMM and MRMs will allow a more direct comparison to the results for the intent-to-treat sample, allows inclusion of subjects that miss some assessments (other than baseline and post-treatment), allows the modeling of complex covariances between the repeated measures, and it assumes MAR rather than MCAR.

Follow Up Secondary Analyses:

Analyses of outcome at FU (Aim 2) will be considered exploratory since subjects may seek additional treatment during follow-up. These analyses will follow the analyses of outcome at post-treatment, except one additional assessment (FU) will be added to these analyses. Since response during FU may not follow the growth curve of the treatment phase, the growth curve

for Aim 2 will be modeled as "piecewise", separately modeling the growth curve during treatment and follow-up. (Analyses of the secondary outcomes at FU will follow the mixed effects ANOVA model described above since these analyses include only 4 total assessments).We will add an additional dummy variable predictor to the analyses for Aim 2, coding whether or not the subject received additional treatment during FU. We will also add the interactions of this "additional treatment" variable with all the other predictors in the analyses to determine if "additional treatment" impacted response to treatment at FU. This analysis will allow us to assess the effect of CBT vs. SE and Yoga vs. SE separately for those who received additional treatment and those who did not. A further analysis will compare the rates at which subjects in the 3 conditions seek additional treatment during the FU period.

Secondary Mediation Analysis for Primary Outcome:

We are interested in mediation of our primary outcome: response at post-treatment. Thus, this analysis will include all assessments through and including post-treatment (but not FU). Our mediation analysis includes 2 independent variables (the contrast of Yoga vs. SE and the contrast of CBT vs. SE) and 3 mediators: mindfulness, vagal tone, and maladaptive cognitions. The "a" paths in the mediation analysis will be the effects of each of the 2 independent variables on each of the 3 mediators. These paths will be derived from three MRMs, one for each mediator as the dependent variable. These MRMs will be identical to the models described above with Time centered at post-treatment. Thus, the effect of each contrast (Yoga vs. SE and CBT vs. SE) will be their effect on each mediator at post-treatment. The "b" paths will be derived from the GLMM model (described above) for differences between treatment conditions at post-treatment, with the dependent variable being "response". The 3 mediators will be included in this growth curve model as additional simultaneous predictors of response. The regression coefficients for the mediators in this analysis become the "b" paths in the mediation analysis (the paths from each mediator to outcome). Significance of mediated pathways will be determined using bias-corrected bootstrap mediation analysis (e.g., Fritz and MacKinnon, 2007 [137]). We predict that changes in mindfulness will mediate changes in outcome over time for patients in the Yoga condition, and changes in cognitions will mediate changes in CBT. Plus, changes in RSA and cortisol may also mediate changes in outcome across conditions.

Missing Data. Although we will make every effort to reduce missingness, it is inevitable that some data will be missing. We will use pattern mixture modeling (Hedeker & Gibbons, 2006; Enders, 2011 [138-139]) and rerun our analyses coding for various missing data patterns (no missing data, early dropouts, late dropouts, FU dropouts, etc.) to determine both if missingness impacts our findings and how the differences between treatment conditions depend on the missing data pattern.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Trained study clinicians blind to randomized treatment assignment (independent evaluators, IEs) will administer diagnostic assessments and rating scales (See Integrity of Diagnostic Assessments).

A number of procedures are in place to assure data integrity and protocol adherence. We will use Research Electronic Data Capture to support direct data entry by patients and study staff. REDCap is a free, secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Web-based surveys rely on a study-specific data dictionary defined by members of the research team with planning assistance from Harvard Catalyst/The Harvard Clinical and Translational Science Center EDC Support Staff. These support staff will then oversee the automated export of study data from REDCap to a relational study database in Microsoft Access 2000, allowing for systematic data querying and checking.

Data will be collected electronically using the Research Electronic Data Capture (REDCap™) software, a free, secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Self-report measures will be completed by participants on a computer, directly into REDCap, thus minimizing errors due to data entry. For clinician-administered measures, trained independent evaluators (IEs) will enter responses directly in REDCap. All IEs will be blind to randomized treatment assignment (See Integrity of Diagnostic Assessments).

To minimize missing data for self-report forms, we will program missed question warnings in REDCap that will alert participants in real-time if they inadvertently skip a question. Participants may then go back and answer any missed questions, or, if they intentionally skipped questions, they may ignore the warning message and continue answer the remaining questions. We will also program real-time range checks in REDCap that generate error messages if a value outside the acceptable range is entered for a given field. To ensure confidentiality, data will be identified in the database only by subject number, visit number, and date of visit. By recording the study data in this manner, the information can be considered 'de-identified' and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 (HIPAA). Any data that is transmitted electronically will be fully encrypted and password protected. Subjects' names will not be entered into the database; each will be uniquely identified only by an ID number. Consent forms, any hard copy PHI, and any study measures that are completed on paper will be kept and filed in locked office cabinets.

At least once a year during the course of the study, we will report on data quality and completeness to the DSMB. At a minimum, the report will include an overview of progress on patient intake and retention; a summary of patient compliance with visits, evaluations, and treatments as described in the protocol; any adverse events or safety concerns that arise; and a summary of the completeness and quality of key data elements needed to characterize patients. These reports will allow the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses. Any DSMB recommendations to improve subject safety, protocol adherence, or data quality will be included in the annual DSMB report. A copy of the annual DSMB report will be sent to the Partners, Boston University, and NYU Medical Center IRBs along with the annual renewal report.

10.2 Data Management

The study biostatisticians (see below) will oversee management of the study database. The principal investigators at NYU and BU, Drs. Simon and Hofmann, are ultimately responsible for the quality of the data collection and overall conduct of the study, and directly

supervise the study coordinators and data management staff. Dr. Simon will oversee the subcontract PI, Dr. Bui, at MGH in the management and quality of data at MGH. Data management will include clinician and patient rated assessments (see assessments), screening data, fidelity data, visit adherence data, IE certification and rater reliability data and safety reporting. Weekly reports will monitor subject enrollment, completion, attrition, and individual subject progress as well as the completion of critical assessments. Additional reports will be done as needed to monitor baseline characteristics, protocol adherence, and other issues of interest.

Research Electronic Data Capture (REDCap) will be used for direct data entry by patients and study staff. REDCap is a free, secure, HIPAA compliant web-based application hosted by Partners HealthCare Research Computing. Web-based surveys rely on a study-specific data dictionary defined by members of the research team with planning assistance from Harvard Catalyst | The Harvard Clinical and Translational Science Center EDC Support Staff. Support staff will oversee the automated export of study data from REDCap to a relational study database in Microsoft Access 2000, allowing for systematic data querying and checking. Biostatistician David Rosenfield, Ph.D., will oversee management of Aparna Keshaviah, M.Sc., and of the study database and data integrity.

All measures that are completed on paper will be entered by the RA into REDCap, and a two pass verification system will be used to minimize any data entry errors. All records in REDCap have a form completion status that may be Incomplete (appears as a red circle in Record Status Dashboard), Unverified (yellow circle), or Verified. The RA initially entering data will save each record entered as Unverified (at which point it will appear as a yellow circle in the Record Status Dashboard). A second RA at each enrolling site will then go into each unverified record, compare each entered value against the paper source document, make any corrections, and then re-save the record as Verified (at which point it will appear as a green circle in the Record Status Dashboard). The color coding system built into REDCap readily allows for identification of unverified records.

Monthly reports will monitor subject enrollment, completion, attrition, and individual subject progress as well as completion of critical assessments. Additional reports will monitor baseline characteristics, protocol adherence, and other issues. Data will be identified only by subject number, visit number, and date of visit such that the information can be considered ‘de-identified’ and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule”) of the Health Insurance Portability Act of 1996 (HIPAA). Any data that is transmitted electronically will be fully encrypted and password protected. Subjects’ names will not be entered; each will be uniquely identified only by an ID number. De-identified data will be transmitted electronically from the MGH site to the NYULMC site in accordance with these guidelines for data analysis purposes.

Consent forms and any hard copy PHI will be kept and filed in secure locked office cabinets.

10.3 Quality Assurance

10.3.1 Training

Trained study clinicians blind to randomized treatment assignment (independent evaluators, IEs) will administer diagnostic assessments and rating scales. The integrity and

reliability of the diagnostic and efficacy evaluations will be established and maintained. All raters will be experienced clinicians who will have undergone specific training to criterion in the use of the study measures. Any new raters will undergo training including rating at least 2 audio or videotaped interviews, then have 2 interviews taped and reviewed for agreement by an expert rater (IE supervisor). The IEs will be M.D., Ph.D. or experienced Masters level diagnosticians with previous research experience with structured interviewing who will receive additional training and certification for this study under the direction of Drs. Simon and Hofmann. In addition to the training procedures, study staff will 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 should also reduce the potential for interviewer drift. A two-level system will be used to maintain the reliability of diagnoses and of other clinical ratings in the study, consisting of weekly supervision and ongoing rating of selected clinical assessments, which will all be digitally recorded. Each month, an independent evaluator (IE) will listen to an assessment performed by another IE associated with the study and independently complete the assessment instruments (SIGH-A, CGI). In addition, each month, all IEs will co-rate an audiotape during a monthly conference call. 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 us 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. Kappa coefficients will be calculated every 12 months. If reliability falls below criteria (ICC $\geq$ 0.8 for CGIs and SIGHA, and 100% agreement on GAD diagnosis), IEs will be retrained.

See Treatment Certification and Supervision Procedures (section 5.2) for training for study treatment providers

10.3.2 Quality Control Committee

The quality control committee will be the executive committee, which will meet weekly and will be comprised of the two PIs, Drs. Hofmann and Simon, the MGH subcontract PI, and the co-investigators, Drs. Khalsa and Hoge, and the biostatistician, Dr. Rosenfield. The members of the committee have a long and fruitful history of collaboration. Drs. Rosenfield and Hofmann have collaborated on numerous empirical studies, and there is a long history of collaboration between Drs. Hofmann and Simon as part of a mutual NIMH grant. Furthermore, there is a history of research collaboration between Drs. Simon and Hoge, Drs. Simon and Bui, and Drs. Hofmann and Khalsa. Dr. Hofmann will chair the executive committee for this grant and bear primary responsibility for maintaining communication between the sites, NCCAM, and a Data Safety and Monitoring Board (DSMB), which will be comprised of three members overseeing safety issues and overall conduct of the study as detailed in the Human Subjects section of the grant proposal. Dr. Simon will oversee the training of independent raters, quality assurance procedures, data management and analysis. All key investigators as well as research staff working on the study will participate in weekly meetings and supervisions. The executive committee will review all publications and presentations derived from data garnered in this grant, in order to ensure its quality. Assignment of publications and other academic products of this project will be decided on by the executive committee, with lead roles equitably rotated among

the three sites. In the unlikely case that disagreements arise, the issue will be resolved by majority decision. If this is not possible, the issue will be referred to the DSMB, which will review the matter and determine an equitable and binding decision. At the end of the trial, each site will receive a cleaned and checked data set – however, all publications and presentations derived from that data in the future will be vetted within the executive committee prior to release.

Biostatistician David Rosenfield, Ph.D., will oversee management of the study database. Monthly reports will monitor subject enrollment, completion, attrition, and individual subject progress as well as the completion of critical assessments. Additional reports will be done as needed to monitor baseline characteristics, protocol adherence, and other issues of interest. In order to ensure confidentiality, data will be identified in the database only by subject number, visit number, and date of visit. By recording the study data in this manner, the information can be considered 'de-identified' and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 (HIPAA). Any data that is transmitted electronically will be fully encrypted and password protected. Subjects' names will not be entered into the database; each will be uniquely identified only by an ID number. Hardcopy data will be kept and filed in locked office cabinets.

10.3.3 Metrics

*1) **Rater Reliability**:*

Each month, an independent evaluator (IE) will listen to an assessment performed by another IE associated with the study and independently complete the assessment instrume*nts (SIGH-A, CGI). In addition, each month, all IE's will co-rate an audiotape during the monthly conference call. Both types of co-ratings (two-by-two and group co-ratings) will be used during supervision to identify reasons for disagreement and improve inter-rater reliability. In addition, ratings will be sent to MGH site to calculate kappa coefficients.* Differences between raters will be discussed during supervision to identify reasons for disagreement and improve inter-rater reliability. These procedures will help us 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. If reliability falls below criteria (ICC $\geq$ 0.8 for CGIs and SIGHA, and 100% agreement on GAD diagnosis), IEs will be retrained. Cross site weekly phone supervision will occur with IEs, addressing any rating problems.

2) **Treatment protocol non adherence**: Fidelity ratings will be performed for all treatments (see treatment fidelity section). Twenty percent of the audiotapes will be rated for adherence and fidelity to ensure that prescribed and proscribed interventions coincide with the assigned groups. During the course of the study, if a therapist does not meet minimum standards - i.e. receives an adherence or competence rating below the certification standard for 2 consecutive sessions ($\leq$5 for adherence, $\leq$3 for competence) - he/she will receive more training from the supervising clinician (Khalsa, Hoge or Hofmann), and the next 2 sessions will be reviewed and must meet certification standards. In the unlikely event therapists do not meet these standards they will be replaced.

4) **Study Early Discontinuation Rates**: At any review, a >20% drop-out / early termination rate will indicate a PI review of procedures.

3) **Data checks**: Any data check resulting in greater than 20% of missing data will trigger PI level review of data procedures

10.3.4 Protocol Deviations

All minor protocol deviations will be recorded in the protocol deviation log and reported yearly to the DSMB and IRB at continuing review. The executive committee will review every 6 months. Any major protocol deviations will be recorded in the protocol deviation log and reviewed with the study PI at weekly meetings and in monthly reports to the executive committee.

10.3.5 Monitoring

Study staff meetings will occur weekly, with PI meetings weekly. Quality control committee meetings will occur monthly. DSMB meetings will occur yearly as noted in the DSMP.
See above.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document has been reviewed and approved by the IRBs of BU, MGH, and NYU.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record. Signed consent forms will be stored in secure files.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the NCCAM, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCAM, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

The executive committee will meet weekly and will be comprised of the two PIs, Drs. Hofmann and Simon, the MGH subcontract PI, Dr. Bui, and the co-investigators, Drs. Khalsa and Hoge, and the biostatistician, Dr. Rosenfield. The members of the committee have a long and fruitful history of collaboration. Drs. Rosenfield and Hofmann have collaborated on numerous empirical studies, and there is a long history of collaboration between Drs. Hofmann and Simon as part of a mutual NIMH grant. Furthermore, there is a history of research collaboration between Drs. Simon and Hoge, Drs. Simon and Bui, and Drs. Hofmann and Khalsa. Dr. Hofmann will chair the executive committee for this grant and bear primary responsibility for maintaining communication between the sites, NIMH, and a Data Safety and Monitoring Board (DSMB), which will be comprised of three members overseeing safety issues and overall conduct of the study as detailed in the Human Subjects section of the grant proposal. Dr. Simon will oversee the training of independent raters, quality assurance procedures, data management and analysis. All key investigators as well as research staff working on the study will participate in weekly meetings and supervisions, and monthly conferences.

13. PUBLICATION OF RESEARCH FINDINGS

The executive committee, chaired by the study PIs (Hoffmann, and Simon) will review all publications and presentations derived from data garnered in this grant, in order to ensure its quality. Assignment of authorship for publications and other academic products of this project will be decided on review of requests for publications with the study data request form by the executive committee, with lead roles equitably rotated among the three sites and final approval resting with the study PIs. In the unlikely case that disagreements arise that cannot be resolved by the study PIs, the issue will be resolved by majority decision. If this is not possible, the issue will be referred to the DSMB, which will review the matter and determine an equitable and binding decision. At the end of the trial, each site will receive a cleaned and checked data set – however, all publications and presentations derived from that data in the future will be vetted within the executive committee prior to release. Any presentation, abstract, or manuscript will be made available for review by all co-authors prior to submission.

All NIH rules for public access of manuscripts will be followed.

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15. SUPPLEMENTS/APPENDICES