Brief CBT for Anxiety and Depression in Pediatric Primary Care (BCBT)

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Project summary:
This study will test whether a brief (12 week) psychological treatment program, based in primary care, can help youths struggling with depression and anxiety. Impact of the program on symptoms and cost-effectiveness will be measured. This will be the first study to assess if anxiety and depression can be treated with one, simple program, and results may help move effective treatments for these serious problems into community practice.

Detailed abstract:
This 5-year project is an interlocking, two-site collaborative R01 to test the effects of a brief cognitive behavioral therapy (BCBT) protocol in a large sample (total N=210) of children and adolescents presenting with anxiety and/or depression in primary care. Depression and anxiety in youth are prevalent and impairing conditions, with a high degree of current and lifetime comorbidity. Targeting the internalizing disorders as a unified problem area is innovative, and in line with calls from the National Institute of Mental Health (NIMH) for new approaches to conceptualizing comorbidity and treating near neighbor disorders. This proposal builds on a successful preliminary study (N=54) in which a pilot version of the BCBT program was well-accepted by patients, families, and clinicians was more efficacious than facilitated referral to specialty mental health care (SMHC). In this new, multi-site R01, we propose to test BCBT in a larger, more diverse sample to establish its utility as a community-based intervention. To this end, internalizing youths identified in primary care practices in San Diego (n=105) and Pittsburgh (n=105) will be randomly assigned to BCBT delivered on-site or facilitated referral to SMHC. Clinical outcomes will be assessed by independent evaluators blind to participant status at 16 and 32 weeks post-randomization (Aim 1). It is hypothesized that BCBT will be superior to SMHC referral in terms of overall clinical improvement (CGI-I < 2) and change in anxiety (PARS) and depression (CDRS-R) symptoms. Response also will be evaluated on brief self-report measures (SCARED, MFQ), as future community care may need to rely more heavily on these types of assessments. In addition, individual trajectories of participants will be examined to understand predictors of treatment response (Aim 2). Based on the depression treatment literature, it is hypothesized that severity of depression symptoms (youth and/or parent) will predict poorer response across treatments but that the BCBT program will still outperform SHMC referral. The effects of ethnicity also will be explored, controlling for differences in socioeconomic status. The proposal is noteworthy in adopting a deployment-focused model and testing this intervention early in its development within a real world context – primary care – likely to be an appropriate setting for future treatment dissemination. In line with this focus, pilot data will be collected on the cost-effectiveness of the program (Aim 3) in order to lay the groundwork for future investigations focused on issues of dissemination, implementation, and real world sustainability. San Diego will serve as the overall coordinating site for the project, and Dr. Weersing will bear final scientific responsibility for the project across all sites.
OVERVIEW

The proposed two-site collaborative R01 will test the effects of a brief cognitive behavioral therapy (CBBT) protocol (8-12 sessions) in a large sample (total N=210) of children and adolescents (age 8-15) presenting with anxiety and/or depression in primary care. Clinical and cost-effectiveness of CBBT will be compared to a plausible public health alternative—enhanced referral to specialty mental health care (SMHC). The two coordinating institutions and principal investigators are: (a) the San Diego State University Research Foundation (San Diego), V. Robin Weersing, PhD (PI), and (b) Western Psychiatric Institute and Clinics (Pittsburgh), David Brent, MD (PI). The proposed project builds on a pilot study (N=60; Weersing, PI) demonstrating feasibility of study procedures and intervention model (see Preliminary Studies). The proposed two-site, randomized trial is the next logical step in the development, evaluation, and dissemination of this program to a population of youth with high need for effective mental health services. The collaborative R01 mechanism leverages the investigators’ expertise across sites and will allow for a more scientifically complete project with a more diverse sample of participants than could be achieved by either site alone.

Rationale for Collaborative Mechanism

The dual-site design leverages the diverse samples of youth and the investigator expertise and institutional infrastructure available in San Diego through San Diego State University (SDSU), the Child and Adolescent Services Research Center (CASRC), and the Minority Research Infrastructure Support Program (M-RISP) and in Pittsburgh through Western Psychiatric Institute and Clinics and the Clinical and Translational Science Institute (CTSI) of the University of Pittsburgh. We briefly discuss the benefits of collaboration in each domain.

Diversity of sample. At both sites, the investigators have developed relationships with primary care practices focused on serving ethnically diverse and low-income patients. For example, in San Diego, we have built a collaboration with Neighborhood Healthcare (NH), a non-profit community health organization that serves individuals with health care access problems (e.g., the uninsured). In our San Diego recruitment plan, we have included two NH practices that provide care to low-income patients (73% of patients below poverty line) of predominantly Caucasian (56%) and Hispanic (42%) background. Similarly, in Pittsburgh, we have developed a relationship with Children’s Community Pediatrics (CCP) - Pittsburgh Pediatrics and the Children’s Hospital of Pittsburgh Primary Care Center, which serve a high proportion (40% and 71%, respectively) of African-American families. Across both sites, thus, we will be able to enroll a much more diverse sample of participants than would be available at either site alone.

Investigator expertise and institutional infrastructure. The sites also bring together complementary areas of scientific expertise and institutional resources. Dr. Weersing and her collaborators and consultants (Lynch, Leslie, Miranda, Hoagwood) through the San Diego site have extensive background in youth mental health services and effectiveness research, relevant for the practice-based testing of this CBBT protocol. Dr. Weersing’s work focuses on the effectiveness of interventions for internalizing youth in real word settings; she is the developer of the BCBT program and the PI of the pilot treatment development study (see Preliminary Studies). Dr. Weersing also has served as a co-investigator (co-I), manual author, and clinical supervisor for a CBT trial targeting youth at-risk for depression, recruited from health maintenance organizations (MH064503; Brent, PI), and a CBT trial for anxious youths with comorbid abdominal pain, recruited from gastrointestinal and primary care clinics (MH073769; Campo, PI). Dr. Lynch (co-I) has led the economic analysis of five adolescent depression trials and will conduct cost-effectiveness analyses of the CBBT program. Dr. Leslie (consultant) is a developmental-behavioral pediatrician and mental health services researcher with a history of successful data collection in the San Diego pediatric practice community (MH064816; see Preliminary Studies) and will be available to consult to the implementation of the proposed project. Since our prior submission, Dr. Kimberly Hoagwood has joined the project as a consultant to provide a broad perspective on treatment dissemination, and Dr. Jeanne Miranda will be available to consult on recruitment and retention of ethnic minority families, cultural issues in assessment, and interpretation of culture and ethnicity effects (see Response to Reviews).

Dr. Brent and the Pittsburgh team have a long record of successful implementation of multi-site studies and clinical trials in youth mood disorders. Under Dr. Brent’s direction, Pittsburgh has served as the data coordination and assessment training center for seven multi-site investigations over the past decade. Dr. Brent has served as a PI in three clinical trials, including serving as the lead investigator in a six-site trial of treatment resistant adolescent depression. He is an internationally recognized expert in youth depression and suicidality, and provides senior leadership to complement and support Dr. Weersing’s first R01 submission. Furthermore, Drs. Brent and Weersing have worked together in the past (discussed below) and collaborated in the development of a Practice-Based Research Network (PBRN) of primary care offices, which serve as the recruitment network for Pittsburgh data collection.
Coordination Between Sites

History of collaboration. The two PIs have a well-established history of long-distance, collaborative research. Dr. Weersing was a postdoctoral fellow at Pittsburgh, under the mentorship of Dr. Brent. She has served as a co-I on Dr. Brent’s Advanced Center for Interventions and Services Research for Early-Onset Mood and Anxiety Disorders (MH066371; Brent, PI), and co-PI on the Prevention of Depression in Adolescents (POD) study, a four-site collaborative R01 (MH064503; Brent, PI). Both of these successful collaborations were coordinated long-distance, after Dr. Weersing accepted a faculty position outside of Pittsburgh. Dr. Brent also has served as a co-I on Dr. Weersing’s projects, including the pilot treatment development project designed to assess the feasibility of the proposed study procedures and intervention model (see Preliminary Studies). They have collaborated on research papers (Weersing, Iyengar, Birmaher, Kolko, & Brent, 2006) and critical scientific reviews specifically focusing on issues in treatment development and dissemination (Brent & Weersing, 2007, 2008; Weersing & Brent, 2003, 2004, 2005, 2006;).

Site responsibilities. Each site will implement the identical research protocol and contribute 105 participants. In addition to these shared responsibilities, we specialize some project functions and staff by site to leverage the complementary expertise of investigators in San Diego and Pittsburgh. San Diego will bear primary responsibility for study coordination as well as training and supervising therapists and monitoring the implementation of the therapy program in the primary care setting. In turn, Pittsburgh will have additional staff in and responsibility for data management and statistical analysis.

Coordination plan. In the first four months of award, the San Diego team will travel to Pittsburgh to conduct therapist training and to be trained by the Pittsburgh team in the assessment protocol. An in-person re-training has been scheduled for Year 03 to maintain reliability of procedures. Over the course of the award, activities will be coordinated by four cross-site standing committees, focused on Project Management (PM), Data Management (DM), Intervention Delivery (ID), and Health Service Implementation (HSI). Each committee will have representatives from San Diego and Pittsburgh and will include project staff relevant to the mission of the group. The PM committee (Weersing, chair) will oversee project operations, including budget, personnel, regulatory compliance, participant safety monitoring, and timeline and study progress. Weekly PM conference calls will include both PIs and Project Coordinators (PC). The DM committee (Brent, chair; Iyengar, co-chair) will oversee data collection and entry and statistical analyses. We anticipate weekly DM calls, with call agenda and membership shifting from focus on assessment training in Year 01, data management in Years 02-04, and analysis in Year 05. The ID committee (Weersing, chair) will monitor quality of BCBT implementation and serve as a venue for cross-site case consultation. We anticipate weekly ID calls in Years 01-04. Finally, we also plan to convene a monthly HSI conference call to serve as a forum to discuss issues in primary care implementation. In Year 05, focus of this group will shift to cost-effectiveness analyses and interpretation. The HSI committee will be chaired by Dr. Lynch, with Drs. Weersing and Leslie and the site PCs as regular members of the group. Drs. Miranda and Hoagwood will join the HSI call in Year 01 to aid in start-up and in Year 05 to consult on analysis and interpretation of results. They will be available to consult to the PIs and the HSI committee on an ad-hoc basis in intervening years.

Significance

The proposed two-site collaborative R01 will be the first large-scale test of a promising new integrated treatment program aimed at youths with anxiety and/or depression. Depression and anxiety in youth are prevalent and impairing conditions, with a high degree of current and lifetime comorbidity. An integrated BCBT program targeting the internalizing disorders as a unified problem area is innovative, and in line with calls for new approaches to conceptualizing comorbidity and treating “near neighbor” disorders. The proposed project is well-powered to test its primary aim of clinical effectiveness (Aim 1) and to assess treatment predictors and moderators (Aim 2) that may aid in the personalization of the treatment over time (e.g., severity of depression symptoms, ethnicity). The proposal is noteworthy in adopting a deployment-focused model and testing this intervention early in its development within a service context – primary care – likely to be a setting for future dissemination. In line with this focus, we propose collecting pilot data on cost-effectiveness of the program (Aim 3) to lay the groundwork for future investigations focused on dissemination, implementation, and real world sustainability. The two-site design of this proposal builds on the experience and leadership of the Pittsburgh site in conducting high-quality clinical trials and the experience of the San Diego team in conducting practice-based research; furthermore, inclusion of both sites should allow for the recruitment of a much more diverse sample of youth and families than is available at either site alone.
2. SPECIFIC AIMS

This proposal is part of an interlocking, two-site collaborative R01 designed to test the effects of a brief cognitive behavioral therapy (BCBT) protocol (8-12 sessions) in a large sample (N=210) of children and adolescents (age 8-15) presenting with anxiety and/or depression in primary care.

Development of an integrated BCBT treatment for youth depression and anxiety seems justified on both theoretical and public health grounds. Mood and anxiety disorders in youth are disabling, distressing, and prevalent (e.g., Bell-Dolan, Last, Strauss, 1990; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993). Depression and anxiety share several common etiological factors (e.g., Axelson & Birmaher, 2001; Eaves, Silberg, & Erkanli, 2003; Kendler, 1996), and the level of comorbidity is extremely high (Angold, Costello, & Erkanli, 1999). In addition, anxiety and depression respond to similar interventions. Focusing on psychosocial treatment, there is copious evidence that CBT can produce significant benefit in mild to moderately impaired samples (Compton et al., 2004), and the core CBT techniques used to treat the two conditions are similar. Despite this overlap in pathology and treatment, there has yet to be an experimental test of an integrated intervention designed to address anxiety, depression, and their combination in pediatric populations.

From a public health perspective, availability of an effective BCBT for internalizing youths would seem valuable, as service settings struggle with limited sessions and resources available to train clinicians in multiple protocols. This need may be particularly pressing in an increasingly important setting – primary care. As with adults, primary care has become a de facto part of the youth mental health system. Most youths visit primary care at least once annually (Costello et al., 1988); families look to primary care clinicians (PCCs) for guidance on psychosocial problems (Horwitz, et al., 1992), and PCCs write the majority of youth psychotropic prescriptions (Libby et al., 2007). Surveys indicate that PCCs view internalizing disorders as their clinical responsibility (Olson et al., 2001), but many families and PCCs are unwilling to consider antidepressants (Rushton, Clark, & Freed, 2000), a preference reinforced by the FDA black box warning (Rosack, 2005). Indeed, the public health salience of a brief, effective psychosocial treatment for internalizing youth is heightened by documented declines in the diagnosis of depression and pharmacological treatment of pediatric mood disorders in primary care since the FDA warning – declines that have occurred alongside an increase in the adolescent suicide rate (Libby, Orton, & Valuck, 2009; Gibbons, Hur, Bhaumik & Mann, 2006).

To address these scientific and public health needs, over a 5 year period, we will randomly assign 210 youth (105 per site) with diagnoses of anxiety, depression, or both to (a) BCBT delivered in primary care or (b) enhanced referral to specialty mental health care (SMHC). Outcomes will be assessed by independent evaluators (IE) blind to participant status at 16 and 32 weeks post-randomization. Study aims, procedures, and intervention model have been informed by a pilot feasibility study (see Preliminary Studies section).

2.1. Primary Aims

Aim 1. To test the effects of the BCBT program compared to enhanced SMHC referral. We will probe the effects of the protocol in three domains – global clinical improvement (Clinical Global Impression Scale; Guy, 1976), anxiety (Pediatric Anxiety Rating Scale; RUPP, 2002), and depression (Children’s Depression Rating Scale-Revised; Poznanski & Mokros, 1996). We hypothesize that BCBT in primary care will be superior to SMHC referral across domains at post-treatment (Week 16) and follow-up (Week 32) assessments. In addition, we will evaluate response on the Screen for Child Anxiety and Related Disorders (Birmaher et al., 1999) and the Mood and Feelings Questionnaire (Wood, Kroll, Moore, & Harrington, 1995), as future community care may need to rely more on brief self-report measures of anxiety and depression.

Aim 2. To examine variability in treatment response and identify potential predictors and moderators of treatment effects (e.g., youth depression severity, parental depression, ethnicity). In addition to assessing the main effects of the intervention, we plan to examine the individual outcomes and trajectories of participants and seek to understand the level of variability in treatment response. Based on the youth treatment literature, we hypothesize that severity of depression symptoms (youth and/or parent) will predict poorer response across treatments but that the BCBT program will still outperform enhanced SHMC referral. We also will explore whether ethnicity predicts treatment response.

2.2. Secondary Aim

In addition, we propose secondary analyses focused on developing initial estimates of stakeholder-relevant outcomes of cost and service utilization. Our goal is to collect information needed to plan larger-scale,
Aim 3. To develop initial estimates of the cost-effectiveness of the BCBT protocol compared to a plausible public health alternative (enhanced SMHC referral). For youths in both arms of the study, we will assess the cost per (a) depression-free-day (DFD), (b) anxiety-free-day (AFD), (c) psychopathology-free-day (PFD), and (d) quality-adjusted life year (QALYs). We hypothesize that the cost per outcome (e.g., cost per PFD) achieved by BCBT will be lower compared to SMHC referral at Week 16 and Week 32 follow-up. In addition, we will develop an estimate of the start-up costs associated with BCBT implementation, excluding research-specific activities, to aid in the design of future trials and provide data with immediate practice relevance.

3. BACKGROUND AND SIGNIFICANCE

3.1. Why Focus Broadly on “Internalizing” Disorders?

Prevalence of depression and anxiety. Mood and anxiety disorders in childhood and adolescence are disabling, distressing, and prevalent. By some estimates, up to 20% of youths in the United States may meet criteria for an anxiety disorder at any given time (Bell-Dolan et al., 1990), and more than 1 in 5 will likely suffer an episode of depression before the end of puberty (Lewinsohn et al., 1993). Furthermore, the level of comorbidity between anxiety and depression in youth is extremely high. In community samples, between 25-50% of youths with depression will also meet criteria for an anxiety disorder, and 10-15% of those with a primary anxiety disorder will be concurrently depressed (Angold et al., 1999). In outpatient mental health samples, rates of comorbidity may be as high as 70% (Birmaher et al., 1996), and our pilot work in primary care yields comparable data (80% of depressed youth met criteria for anxiety, see Preliminary Studies).

Functional impairment and adverse long-term outcomes. Depression and anxiety interfere with youths’ ability to form close and meaningful friendships, impair school performance, and increase the risk of suicide attempt and completion (Gould et al., 1998; Rohde, Lewinsohn, & Seeley, 1994; Strauss, Frame, & Forehand, 1987). In addition, the negative effects of early-onset of mood and anxiety problems may propagate forward through development and substantially interfere with youths’ adult potential, including lower educational attainment, poor work history, and adult substance abuse (Keller, Wunder, Beardslee, Schwartz, & Roth, 1992; Rohde et al., 1994; Weissman et al., 1999). Furthermore, there is evidence that youth anxiety may be a risk factor for depression in adolescence and adulthood and that treatment of anxiety may prevent the development of recurrent depressive disorders (e.g., Hayward, Killen, Kraemer, & Taylor, 2000; Hettema, Prescott, & Kendler, 2003; Pine, Cohen, Gurley, Brook, & Ma, 1998).

Impact on health systems. In addition to the personal impact of these disorders, youths with mood and anxiety problems come with added costs to health systems. Anxiety and depression in youth are associated with increased medical visits (Zuckerman et al., 1996) and inpatient surgeries (Weissman et al., 1999) and are frequently comorbid with somatic symptoms that prompt use of services, such as recurrent abdominal pain and headaches (Campo et al., 1999). In addition, experience of depression is correlated with poorer health (e.g., increased mortality following heart attack; Katon, 2003) and health risk behaviors (e.g., risky sexual behavior; Kosunen, Kaltiala-Heino, Rimpela, & Laippala, 2003). Despite the apparent cost of these problems, little is known about the cost-effectiveness of preventing or treating internalizing disorders in youth (Lynch & Clarke, 2006; Romeo, Byford, & Knapp, 2005). To date, one economic evaluation has suggested short-term cost-effectiveness for adolescents receiving a CBT depression prevention program (Lynch et al., 2005).

Shared etiology and response to treatment. Studies in the developmental psychopathology of internalizing disorders suggest that the co-occurrence of anxiety and depression may be due to shared genetic, neurobiological, or parenting-related factors (see Axelson & Birmaher, 2001). Response to treatment provides further, indirect, evidence of shared mechanisms. Both depression and anxiety respond to selective serotonin reuptake inhibitors (SSRIs; e.g., Emslie et al., 2002) and to CBT (Compton et al., 2004). Examining the course of CBT, mood and anxiety symptoms move in synchrony, even when treatment is ostensibly targeting either youth anxiety (Kendall, 1994) or adolescent depression (e.g., Weisz, McCarty, & Valeri, 2006).

Findings such as these have prompted calls for the development of a unified treatment for the emotional disorders (Barlow, Allen, & Choate, 2004), with the hope that an integrated treatment for internalizing disorders might prove more efficient for (a) patients struggling with several “near-neighbor” problems, (b) providers seeking to learn and deliver evidence-based treatments in their practice, and (c) educators and health care payers seeking to train the next generation of mental health service providers. The development of an
integrated treatment is facilitated by the fact that many of the CBT techniques used to treat depression and anxiety are functionally the same. We discuss these technique-level similarities further in the description of the conceptual model underlying the BCBT treatment program.

3.2. Why Build on Cognitive Behavioral Therapy?

As discussed previously, depression and anxiety respond to very similar interventions, most notably the SSRIs and CBT. Our choice to use CBT as the base for our intervention was shaped by several factors.

Positive effects of CBT on anxiety. CBT has shown consistently positive effects in the treatment of youth anxiety and phobias, with some of the highest reported response rates in the psychosocial treatment literature (Compton et al., 2004; James, Soler & Weatherall, 2005). Interpersonal psychotherapy, an effective psychosocial treatment for adolescent depression (Mufson, Weissman, Moreau, & Garfinkel, 1999), has not been tested in younger populations of depressed youth nor with a primarily anxious sample. CBT also is quite efficacious for adult anxiety disorders (e.g., Gould, Buckmister, Pollack, Otto, & Yap, 1997), indicating the skills may have good applicability and continuity across the lifespan. Finally, although there have yet to be long-term follow-up data on the effects of CBT versus SSRIs in anxious youth (Walkup et al., 2008), the adult anxiety treatment literature suggests that CBT produces effects as good or better than medication at immediate post-treatment and may provide superior protection against relapse (Barlow, Gorman, Shear, & Woods, 2000; Gould, Otto, & Pollack, 1995; Gould, Otto, Pollack, & Yap, 1997).

Positive effects of CBT on depression and placing TADS in context. CBT has a two decade history of positive results in clinical trials for youth depression (Compton et al., 2004) including a landmark trial by the Pittsburgh PI (Brent) indicating that CBT outperforms other psychosocial interventions (family therapy, nondirective therapy) for moderately to severely depressed adolescents (Brent et al., 1997). These positive findings, however, must be tempered by the results of the Treatment for Adolescents with Depression Study (TADS, 2004), in which CBT failed to outperform a pill placebo condition. Given the results of TADS, is the choice of CBT for our integrated anxiety-depression protocol justified?

In our view, the answer is yes, for two main reasons. First, as has been noted elsewhere, the CBT manual developed for TADS may not have been the strongest version of this mode of intervention (Hollon, Garber, & Shelton, 2005; Weersing & Brent, 2006). The TADS manual strove to be comprehensive and to provide a great deal of therapist choice in selecting what specific CBT treatment techniques were used with each case (Curry & Wells, 2005). While intuitively appealing, in practice this may have led many youths to receive a less than optimal dose of core CBT techniques (e.g., behavioral activation) with less central activities dominating the treatment dose (e.g., rekindling attachment). In our manual, we have focused treatment on a small set of core CBT techniques and encouraged youths to practice and gain mastery in these domains.

Second, the TADS sample may have been more severely depressed than the samples in previous CBT clinical trials (TADS, 2004). As part of this argument, it has been proposed that CBT for depression in youth may only work in mild to moderately impaired samples. Given the positive results of the Brent clinical trial of CBT (in a similar sample to TADS), we do not find this line of reasoning completely compelling (Bridge & Brent, 2004). However, if it were the case, this would still support the proposed project, which focuses on primary care treatment of youths, rather than tertiary care of severe, treatment-resistant cases. For the primary care setting, we have developed a brief intervention for mild to moderately impaired youths, with the aim of catching youths earlier in their disease process and intervening before internalizing problems require more extensive treatments. For similar reasons, we are aiming our intervention at school age youth (8-11) and young teens (12-15), who should be earlier in the course of their internalizing trajectory.

From a public health perspective, there may be a great value in targeting brief, psychosocial interventions to this population of younger, less severe internalizing youths. In addition to the results of TADS, a major meta-analysis (Bridge et al., 2007) reported that depression duration is one of the strongest negative predictors of clinical response. Consequently, identification and treatment of youth prior to development of chronic disorder is likely to be more cost-efficient, and, in the long run, yield a course more consistent with normal development.

Greater treatment acceptability. While there is evidence that depression and anxiety respond to CBT and SSRIs, many patients, parents, and providers do not find medication use acceptable (Rushton et al., 2000; Wisdom, Clarke, & Green, 2006) or prefer to begin treatment with a psychosocial intervention before considering medication (e.g., Asarnow et al., 2005). For example, in a randomized treatment study for socially anxious youth, reluctance toward medication use accounted for 44% of study refusals and was especially common among ethnic minority families (Young et al., 2006). Primary care surveys of depressed teens show similar ethnic differences; youths from all groups generally have more favorable views of counseling than
medication, but this preference is stronger in Hispanic and African-American teens (Chandra et al., 2009). Furthermore, much of the data on SSRI acceptability may paint an optimistic portrait, given that many surveys were conducted prior to the public FDA hearings on heightened risk of suicidality for youths taking SSRIs and the resulting black box warning label (US Food and Drug Administration, 2004). As discussed previously, mental health service use data indicate that SSRI prescriptions are markedly down since the black box warning was implemented, and more concerning, that both in the US and the Netherlands, this decline was associated with a concomitant increase in adolescent suicide (Gibbons et al., 2007; Libby et al., 2007; Rosack, 2005).

3.3. Why Primary Care?

Deployment-focused development model. Many commentators and critics of the field have decried the gap between research and practice in mental health and the slow rate of dissemination of empirically tested interventions into active clinical service (e.g., Hoagwood, 2002; Kazdin, 2000; Weisz, Donenberg, Han, & Weiss, 1995). Speeding the process of treatment dissemination is a major priority of NIMH (Blueprint for Change, 2001), and deployment-focused treatment development a central theme in the work of the San Diego PI (see Weisz & Weersing, 1999, for discussion). Accordingly, we have based the first large-scale test of our integrated BCBT program within a clinical service setting that seems well-suited for the treatment of our population of interest – primary care. We do not believe that this intervention would only be appropriate for use in primary care; rather, we hope to ensure that our work is clearly relevant to at least one, consequential, real world service setting. With this in mind, we next review the increasingly important role of primary care in youth mental health and primary care research results from the youth and adult literatures.

Role of primary care in youth mental health. As in adults, primary care has become a de facto part of the mental health system for youth. The majority of youths visit primary care at least once annually (Costello et al., 1988); families look to doctors for guidance on psychosocial problems (Horwitz et al., 1992), and the federal government has called for routine pediatric mental health screening and research on cost-effective care (Office of the Surgeon General, 1999). Primary care clinicians (PCCs) write the majority of prescriptions for psychiatric drugs for youth (Kelleher, Hohmann, & Larson, 1989), although PCCs report reluctance to prescribe psychotropics, and PCCs prefer psychosocial interventions, typically through off-site referral for specialty mental health care (SMHC) counseling (Rushton et al., 2000). Rates of youth depression and anxiety in primary care screening studies are higher than those in community epidemiological surveys (e.g., 35%; Chavira, Stein, Bailey, & Stein, 2004), and internalizing youths use more health services, an effect not explained by differences in physical health status (Zuckerman et al., 1996).

Mental health treatment trials in primary care. In the last decade, there has been a significant upswing in the number of published research reports on primary care interventions for mental health. The vast majority of this work has focused on adult (or geriatric) depression and adopted “quality improvement” (QI) designs, many of which allow patient preference to shape treatment content (e.g., allowing adults in the QI arm to choose psychotherapy or medication). The brief psychotherapies in adult depression QI protocols have included CBT, (Wells et al., 2000), problem-solving programs (Unützer et al., 2002), Interpersonal Psychotherapy (Bruce et al., 2004), and enhanced self-management (Dietrich et al., 2004). Overall, QI programs for adult depression have shown positive effects compared to primary care treatment as usual (Neumeyer-Gromen, Lampert, Stark, & Kallischnigg, 2004), with some evidence of cost-effectiveness (e.g., Liu et al., 2003). In adults, work is beginning to address treatment of anxiety in primary care, with a recent clinical trial showing positive effects for a brief CBT + medication protocol (Roy-Byrne et al., 2005).

The youth literature is at a much earlier stage of development. To date, there are two randomized primary care treatment studies for depressed adolescents: (a) a multi-site QI study comparing enhanced care with patient choice of interventions (with a CBT treatment option) to primary care treatment as usual (Asarnow et al., 2005); and (b) an investigation of CBT+SSRI compared to medication management alone, embedded in a health maintenance organization (Clarke et al., 2005). In their QI investigation, Asarnow and colleagues found that enhanced care was superior to treatment as usual in increasing participants’ access to depression care (i.e., number of sessions) and on improving depression symptoms and quality of life. Results were similar in magnitude to findings in the adult primary care depression literature (Wells et al., 2000). However, unlike the adult literature, the QI intervention did not increase rates of medication use, as depressed teens chose the CBT treatment option within the QI arm. Clarke et al. found that adding CBT to high-quality medication management provided only modest benefits on measures of symptoms and functioning (Cohen’s $d = 0.17$ to 0.20). However, these small improvements occurred as youths significantly reduced their medication use in the CBT+SSRI arm – an unintended consequence of the CBT intervention. In addition, teens in the CBT+SSRI program utilized fewer health care services over one year follow-up, while maintaining the same level of
symptoms as youths in the SSRI arm. Results of both of these studies reinforce survey findings that parents and youth have a preference for psychosocial treatments over pharmacotherapy when given the choice.

3.4. Conceptual Model Underlying Treatment

Taken together, these literatures suggest that (a) **internalizing disorders in youth are a pressing public health problem**; (b) **CBT for anxiety and depression is a promising psychosocial treatment approach** for these syndromes; and (c) **primary care is a significant mental health service setting**, in which it would be valuable to have a brief, psychosocial treatment option for internalizing youths. We next briefly describe the conceptual model underlying our integrated protocol and our approach to treatment development.

**Theories of psychopathology and intervention.** Modern theories of the etiology and maintenance of anxiety disorders focus on the interplay between (a) biological vulnerability to acute stress reactions (e.g., Biederman et al., 1993); (b) experience of uncontrollable stressful life events (e.g., Chorpita, & Barlow, 1998); (c) maladaptive behavioral responses to threat (e.g., avoidance behavior; Dadds, Barrett, Rapee, & Ryan, 1996); and (d) inaccurate, overly-threatening, interpretations of events (e.g., anxious apprehension; Barlow, 1988). In a similar fashion, theories of depression implicate interactions between (a) genetic vulnerability to mood dysregulation in response to stress (e.g., Caspi et al., 2003); (b) experience of stressful life events, with evidence that the threshold for stress-triggered episodes may fall over the course of disorder (e.g., Kendler, Thornton, & Gardner, 2001); (c) maladaptive behavioral responses to stress (e.g., poor interpersonal problem solving skills; e.g., Gazelle & Rudolph, 2004); and (d) inaccurate, overly negative, and hopeless cognitive styles (e.g., Gladstone & Kaslow, 1995). Although not identical, **the similarity of processes implicated in the development and maintenance of mood and anxiety disorders is striking.** In fact, in an elegant analysis of the Virginia Twins Study, Eaves and colleagues (2003) found that (a) anxiety tends to precede depression, (b) there may be a shared diathesis for anxiety and depression, and (c) depression may develop as a consequence of an interaction between environmental stressors and the genetic liability to anxiety.

Not surprisingly, CBT interventions for these conditions contain similar elements and focus most strongly on modifying person-level responses to stress. However, **CBT programs differ markedly in their level of complexity and the number of techniques employed.** For example, a review of CBT manuals for adolescent depression reveals a long list of skill modules across and within treatment protocols, including problem solving, assertiveness training, cognitive restructuring, family communication skills training, relaxation, mindfulness techniques and self soothing, and pleasant activity scheduling and behavioral activation (Weersing, Rozenman, & Gonzalez,, 2009). The list would grow even longer should CBT anxiety techniques be appended. For theoretical and practical reasons, we **have chosen to adopt a parsimonious approach** for our protocol. As discussed previously, it has been hypothesized that the weaker effects of CBT in TADS may have been due, in part, to the breadth of the program. Conversely, “simple” versions of CBT for depression restricted to either the behavioral (e.g., Dimidjian et al., 2006) and/or cognitive restructuring components (e.g., Brent et al., 1997) have shown equal or greater levels of success compared to more complex versions of CBT.

Pragmatically, the constraints of busy, real world service in primary care also limit a comprehensive CBT approach. The average length of mental health treatment in primary care is estimated to be three visits (Asarnow et al., 2005), and analyses of community SMHC services suggest that a third of depressed youths fail to attend at least of 8 sessions of treatment (Weersing & Weisz, 2002a), although receipt of this minimum dose is associated with better outcomes. Fortunately, CBT may have effects on youth depression in as few as four weeks (Ackerson, Scogin, McKendree-Smith, & Lyman, 1998; Renaud et al., 1998). Extant treatments for anxiety disorders last somewhat longer, with the shortest exposure-based interventions lasting 3 to 6 sessions (Compton et al., 2004). Accordingly, we sought (a) to integrate the array of CBT module options into a small set of techniques targeting core aspects of mood and anxiety disorder in youth, and (b) to combine these core components in a brief program designed to fit within these low dose parameters (approximately 8 sessions).

**Core components of CBT.** To select our core intervention components, we turned to the literature for evidence on the relative efficacy of specific CBT techniques, focusing on the child and adolescent treatment literature when available and the adult literature in the absence of evidence from studies with youth. From this review, two techniques emerged as critical – **exposure and behavioral activation.**

There is evidence that exposure may be the central pathway through which psychosocial interventions for anxiety achieve their effects. In the treatment of childhood phobias, exposure alone is as efficacious as more comprehensive CBT protocols (Ollendick & King, 1998), and analysis of the shape of change in CBT for youth anxiety disorders suggests that the majority of symptom improvement occurs in the second half of treatment, during exposure (Kendall et al., 1997). Meta-analyses of the adult treatment literature lend additional support to this view: **CBT and exposure therapy have produced equivalent outcomes** and the total number of
4.2. Improving “Real World” Care for Pediatric Anxiety and Depression

Moving beyond basic efficacy research, Dr. Weersing and colleagues (including Drs. Brent and Lynch) have conducted a series of studies aimed at understanding and improving the real world clinical care of youths with mood disorder. As discussed previously, the first of these trials found that CBT outperformed family and supportive therapies for depressed adolescents (Brent et al., 1997). In addition, anxiety moderated the effects of treatment in this trial, such that CBT performed significantly better than alternate interventions for youth with comorbid Major Depressive Disorder and anxiety (Brent et al., 1998). In the recently completed Treatment of Resistant Depression in Adolescents (TORDIA, MH061835; Brent et al., 2008) trial, 334 depressed adolescents who had not responded to an adequate trial with an SSRI were randomized to one of two medication strategies, with or without supplemental CBT, in a balanced factorial design. The addition of CBT resulted in a significantly higher response rate, across medication cells (55% vs. 41%; d = 0.30; Brent et al., 2008). Although there was a main effect of CBT in this severely depressed sample, adolescents with the highest levels of depression, chronicity, and hopelessness responded less well to the intervention, making a strong argument for trying to intervene much earlier in the course of these youths’ mood disorders. In addition, the particular CBT modules most closely associated with clinical improvement were assertiveness training and problem-solving (and not cognitive restructuring), again supporting the use of a slimmed down CBT that focuses on behavioral and problem solving targets, as planned for our current project. Taken together, these clinical trials form a strong scientific base for the development and testing of our BCBT protocol for internalizing disorders. This body of work also clearly demonstrates the capacity of the Pittsburgh site, under Dr. Brent’s leadership, to successfully complete major treatment studies in youth mood disorders.

4.1. Establishing the Efficacy of Interventions for Adolescent Depression

Dr. Brent and colleagues have conducted several major clinical trials testing the efficacy of interventions for adolescents with mood disorder. As discussed previously, the first of these trials found that CBT outperformed family and supportive therapies for depressed adolescents (Brent et al., 1997). In addition, anxiety moderated the effects of treatment in this trial, such that CBT performed significantly better than alternate interventions for youth with comorbid Major Depressive Disorder and anxiety (Brent et al., 1998). In the recently completed Treatment of Resistant Depression in Adolescents (TORDIA, MH061835; Brent et al., 2008) trial, 334 depressed adolescents who had not responded to an adequate trial with an SSRI were randomized to one of two medication strategies, with or without supplemental CBT, in a balanced factorial design. The addition of CBT resulted in a significantly higher response rate, across medication cells (55% vs. 41%; d = 0.30; Brent et al., 2008). Although there was a main effect of CBT in this severely depressed sample, adolescents with the highest levels of depression, chronicity, and hopelessness responded less well to the intervention, making a strong argument for trying to intervene much earlier in the course of these youths’ mood disorders. In addition, the particular CBT modules most closely associated with clinical improvement were assertiveness training and problem-solving (and not cognitive restructuring), again supporting the use of a slimmed down CBT that focuses on behavioral and problem solving targets, as planned for our current project. Taken together, these clinical trials form a strong scientific base for the development and testing of our BCBT protocol for internalizing disorders. This body of work also clearly demonstrates the capacity of the Pittsburgh site, under Dr. Brent’s leadership, to successfully complete major treatment studies in youth mood disorders.
with anxiety and depression, including work to (a) define mechanisms of psychotherapy action (Gaynor, Weersing, Kolko, Birmaher, Heo, & Brent, 2003; Southam-Gerow et al., 2001; Weersing & Weisz, 2002b) and models of treatment used in community care (Weersing, Weisz, & Donenberg, 2002), (b) test effectiveness of community therapies (Weersing & Weisz, 2002a; Weersing & Weisz, 2005), (c) assess the clinical and cost-effectiveness of CBT in real world clinical service conditions (Weersing, Iyengar, Birmaher, Kolko, & Brent, 2006; Lynch et al., 2005; Lynch et al., 2006), and (d) develop short “core component” CBT materials for depressed and anxious youth. We review in detail those studies that (a) highlight the importance of developing interventions for anxiety and depressive disorders that are amenable to being disseminated to real world settings and (b) provide reassurance that enhanced referral to specialty mental health care (SMHC) in the proposed study is a reasonable, realistic, and interesting “public health” control condition.

What is typical SMHC care for youths with anxiety and depression? As a first step in investigating the effectiveness of youth psychotherapy in community settings, Drs. Weersing, Weisz, and Donenberg (2002) developed the Therapy Procedures Checklist (TPC) to quantify the techniques used by therapists in typical community care. The TPC asks therapists to rate the extent to which they employ techniques drawn from the three most common therapeutic approaches with youth: psychodynamic, cognitive, and behavioral. The TPC is being used to assess the content of SMHC in over a dozen dissemination studies, and has been translated into three languages for use in international research. In national surveys, Dr. Weersing has used the TPC to map out youth therapy practice patterns. An eclectic picture emerges, with youth therapists employing a high level of psychodynamic technique use, supplemented by some cognitive and a few behavioral techniques. SMHC therapists also report little use of cognitive or behavioral interventions for childhood disorders for which CBT is considered “best practice” treatment. For example, in a sample of SMHC youth with anxiety disorders, 76% of youth did not receive any training in relaxation skills and 81% were not provided any form of exposure therapy (Weersing, Weisz, & Gonzalez, 2009).

Does community SMHC care for youth depression and anxiety work well? Given these differences in technique use between research and practice settings, are effects of community therapy comparable to the effects of CBT in clinical trials? To address this question, Dr. Weersing and colleagues tracked the outcomes of youths who met research diagnostic criteria for Major Depressive and/or Dysthymic Disorder, from their time of intake into community SMHC through a two year follow-up (Weersing & Weisz, 2002a). At intake, SMHC youth exhibited depression symptoms as severe as youth in clinical trials. The median number of sessions was also similar to that of the average CBT package. Despite these similarities, there were substantial differences in depression recovery. Youth treated in clinical trials showed steep improvements in their depression symptoms within three months, and these improvements were maintained over follow-up. Depressed youth in SMHC had much shallower symptom trajectories, and the mean symptom slope for community treatment more closely resembled the clinical trial control conditions than the CBT benchmarks. Dr. Weersing is currently analyzing data from a parallel study of the outcomes of SMHC care for youths with anxiety (Weersing et al., 2009). At this point, the data seem to tell the same tale. Anxious youths in SMHC and in CBT clinical trials appear to have quite similar internalizing symptom profiles (Southam-Gerow, Weisz, & Kendall, 2003). However, despite starting at the same level of severity, two years after treatment (long term follow-up), the rate of anxiety disorder is over four times higher in SMHC youths.

Can CBT work outside of clinical trials? To begin addressing this question, Drs. Weersing and Brent collaborated on an investigation of CBT delivered in a tertiary SMHC setting – the Services for Teens at Risk (STAR) Center, a specialty outpatient service for depressed, anxious, and suicidal adolescents based in Pittsburgh. The Center uses CBT as its psychosocial intervention model, and, upon joining STAR, therapists are extensively trained and supervised in CBT techniques. However, therapists operate autonomously once they are senior clinicians, and STAR uses a broader range of providers to deliver CBT than most clinical trials, including social workers and nurses. STAR also treats a broader range of youths, including teens with comorbid eating disorders and substance abuse. In this setting, depressed youths experienced significant symptom improvement approximately 6 months after intake (Weersing et al., 2006). This time to recovery is almost twice as long as in CBT clinical trials; however, it is half as long as the rate of improvement in eclectic, non-CBT community care, as described previously. These data suggest that adapting and applying CBT in real world service settings may lead to improvements in depression outcome over typical SMHC.

Can CBT protocols be made more “practice ready”? Based on these promising findings on the clinical and cost-effectiveness of CBT, we have begun studying the development of short CBT protocols, optimized for use in community practice settings (in collaboration with Drs. Kimberly Hoagwood and Alan Kazdin). We have combined data from meta-analysis and literature review (Weersing & Weisz, 2002b), expert consensus, and practitioner surveys to identify core CBT techniques. Expert ratings converge on three core CBT components
for youth depression—cognitive restructuring, behavioral activation, and problem solving skills training. While experts considered these techniques important for good outcomes, they varied in ratings of (a) how suitable these techniques are for “real world” depressed youth, and (b) the extent to which they can be taught to non-experts. **Cognitive restructuring is rated as being the most difficult to learn, in contrast to behavioral activation and problem solving skills, which were rated highly in terms of both efficacy and trainability.**

In our analog training studies, therapists have fared much better in learning and applying behavioral techniques than in understanding and using cognitive restructuring. As discussed in the Background and Significance section, these data dovetail with findings in the adult literature that behavioral activation alone may be as effective as full CBT for depression and that behavioral components of CBT for anxiety (i.e., exposure) may carry the bulk of the outcome variance. These findings also are consistent with the recent results of the multi-site TORDIA study (Brent PI; see Preliminary Studies), in which problem solving skills were closely associated with clinical change. **Taken together, these findings highlight the practicality of testing a “user friendly” BCBT for internalizing symptoms that emphasizes behavioral strategies.** Based on this work, we created draft BCBT manuals for anxiety and depression and tested these in primary care.

### 4.3. Preliminary Test of Draft BCBT Materials

**In preparation for this proposal, we created preliminary BCBT intervention materials and began testing the program with a sample (N=60) of anxious and depressed youths (age 8 to 17) drawn from primary care.** In this initial pilot, we created two parallel, 8-session BCBT manuals, one for youths with a primarily depressed presentation and one for youths with a primarily anxious profile. These manuals were a first step toward full treatment integration and differed only in minor details of psychoeducation (e.g., increased discussion of “fight or flight” in the anxiety protocol) and in the framing of the engagement and practice portion of the intervention (i.e., framed as graded exposure for anxiety and graded activation in depression). In practice, the majority of youths received an integrated anxiety-depression protocol, especially since 80% of depressed youths also met criteria for a diagnosable anxiety disorder (see Appendix, Weersing et al., 2008).

**Recruitment and assessment procedures.** To test our proposed design and procedures, **we based the delivery of BCBT in two primary care practices** in the same Practice Based Research Network (PBRN) infrastructure that we plan to employ for the Pittsburgh recruitment for the proposed project. **Youths were identified and referred by their physicians,** who documented verbal consent for the project to contact the family. Eligibility was assessed at a research baseline interview, and youths included who: (a) were age 8 to 17 years; (b) met diagnostic criteria for Major Depression, Dysthymia, or Minor Depression and/or met full or probable (missing one, non-core symptom) diagnostic criteria for Separation Anxiety Disorder, Generalized Anxiety Disorder, Social Phobia, or Specific Phobia; and (c) lived with a consenting legal guardian. To enhance generalizability, we excluded only youths who required treatment other than BCBT, namely youths with (a) bipolar disorder, psychosis, suicidal ideation with plan, post-traumatic stress disorder (PTSD), substance dependence, or mental retardation; (b) experience of recent physical or sexual maltreatment; (c) unstable physical illness (e.g., uncontrolled diabetes); or (d) current participation in an alternate intervention for the target conditions (e.g., antidepressant use with dose change within the last four weeks). Eligible youths were assigned to BCBT or SMHC referral, with block randomization on gender, severity, and medication use.

**Delivery of BCBT.** BCBT was delivered by two therapists, a Master’s-level social worker and a nurse-practitioner. The PI (Weersing), a Ph.D.-level clinical psychologist, reviewed digital recordings of all sessions for the first 3 anxious and 3 depressed cases for each therapist and provided weekly one hour phone supervision per therapist. After three cases, the PI listened to the first session for each participant and reviewed other sessions as requested by the treating clinician (approximately 25% of sessions).

**Enrollment data and sample characteristics.** A total of 84 youths were referred to the project. Of these, 14 declined to attend the baseline interview, and 10 were excluded at baseline (2 for suicidality, 2 for PTSD, 2 for insufficient symptoms of...
anxiety/depression, 1 for failure to document consent of guardians [joint custody], and 3 for requesting services not provided by the project). The remaining 60 youths (71% enrolled of total referred) were randomly assigned to BCBT (n=31) or SMHC referral (n=29), with 25 youths classified as primarily depressed and 35 as primarily anxious. This distinction, however, is somewhat misleading, as 20 of the 25 depressed participants met diagnostic criteria for at least one anxiety disorder, and parent and youth report of anxiety symptoms on the SCARED were indistinguishable when comparing the depressed versus anxious group of participants. Participants were predominantly female (67%), school age or young teen (68%, age 14 or below), Caucasian (97%), and from “working class” families (88% ≤ 4, Hollingshead SES). Youths were generally medication-free (78%) and met full (88%) versus probable criteria for disorder at a mild (40%) or moderate (45%) level of severity at baseline. Youths also presented with comorbid disruptive behavior (18% ODD) and attention (8% ADHD) problems.

Clinical outcomes. As can be seen in Figure 1, at post-treatment, significantly more youths who received BCBT were “much” or “very much” improved on the CGI-I. Across diagnoses, nearly 75% of BCBT youths were rated as substantially improved, with 59% no longer rated as being within the “ill” range (CGI-S < 3). Significantly fewer SMHC youths (33%) were rated as substantially improved, and even fewer fell within the normal range (22%). These results parallel significant post-treatment findings for random-effects regression analyses on depression-specific (e.g., CDRS-R) and anxiety-specific (e.g., SCARED) scales, blocked by primary diagnosis, and for analyses of depression-free-days (DFD). Differences in anxiety-free-days also favored BCBT, though results were not statistically significant in this pilot sample.

While BCBT was superior to SMHC referral at post-treatment (Week 12), by follow-up, these differences were no longer statistically significant. This appears to be due to relapses within BCBT (n=6) and late improvement in SMHC (n=7). We investigated several explanations for this pattern of results. First, we tested whether SMHC youths experienced delay in receiving services, and if SMHC outcomes at Week 24 should be viewed as a lagged treatment effect. As can be seen in the table below, a larger percentage of SMHC youth (41%) never attended therapy compared to BCBT (3%). However, number of sessions and outcome were not correlated in BCBT or SMHC, and, within SMHC, improvement over follow-up was not predicted by (a) receiving versus not receiving treatment or (b) receipt of a “minimum dose” of at least five sessions.

<table>
<thead>
<tr>
<th>Week 0 to Week 12</th>
<th>Week 12 to Week 24</th>
<th>Cumulative Sessions</th>
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<tbody>
<tr>
<td></td>
<td>0 sessions</td>
<td>1 to 4</td>
</tr>
<tr>
<td>BCBT</td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>SMHC</td>
<td>44%</td>
<td>45%</td>
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Second, we sought to determine if our short BCBT protocol may be too brief for some youths in the pilot sample. The data did support this hypothesis. BCBT youth who were improved at post-treatment but who relapsed by six-month follow-up had significantly higher CGI severity scores at post-treatment, compared to BCBT youths who maintained their “improved” status. These findings dovetail with data from depression clinical trials suggesting the importance of treating symptoms to remission, not simply to improvement, and conversely, the high likelihood that youth with subsyndromal symptoms of depression are likely to relapse (Birmaher et al., 2000; Brent, Birmaher, Kolko, Baugher, & Bridge, 2001; Clarke et al., 2005). In light of these findings, we have revised our BCBT treatment manual for the proposed project to include up to four additional “booster” sessions for BCBT youth who are still symptomatic or substantially impaired at the end of the core 8 sessions. This approach is consistent with results from Clarke et al. (1999), in which the addition of booster sessions resulted in consolidation of symptomatic improvement, and with Kroll, Harrington, Jayson, Fraser and Gowers (1996), in which booster sessions of CBT markedly reduced the risk of a depressive relapse.

Taken together, we view results of the pilot study as supporting the feasibility of our study design and procedures and as providing promising data on effectiveness of an integrated BCBT protocol for internalizing disorders. This study has allowed us to pilot our recruitment and assessment procedures and training and supervision protocols. As a result of this experience, we have refined our intervention manual and are prepared for a larger test of the program that will enable us to probe for individual differences in treatment response (Aim 2) and assess broader mental service system and economic outcomes (Aim 3).

4.4. Health Services Research and Primary Care Studies

Cost-effectiveness of mental health interventions. Dr. Lynch is leading the cost-effectiveness analyses (CEA) for four randomized controlled trials of interventions for depressed adolescents: (a) a six-site study of
interventions for treatment resistant depression (TORDIA; MH61869; Brent, PI), (b) a four-site trial of a CBT prevention program for at-risk teens (MH6454; Brent, PI, Weersing, co-I), (c) a single-site study of CBT + antidepressant treatment in primary care (HS10535; Clarke, PI), and (d) a single-site study of CBT for youths who refuse antidepressants (MH073918; Clarke, PI). As discussed previously, Dr. Lynch also performed the CEA of a depression prevention project with a population of adolescent offspring of depressed parents enrolled in a health maintenance organization (Clarke et al., 2002; Lynch et al. 2005).

**Primary care research infrastructure.** Both sites have relevant experience and established site-specific research infrastructure in pediatric primary care. Our consultant to the San Diego site, Dr. Leslie, serves as the PI of the Children’s Care Connection (C3), a developmental and mental health screening program funded through California’s Proposition 10 program and based in a range of real world youth service settings. Since its inception in 2001, C3 has collaborated with over 50 physician practices and community clinics, including over 200 physicians. Overall the C3 project has provided 4,503 screenings and 2,007 assessments as a result of direct referrals from pediatric and family practices in the San Diego County region. In 2006 alone, there were 558 screenings and 200 assessments resulting from physician referrals. In addition, Dr. Leslie was the PI of an NIMH-funded study using a quality improvement model to examine implementation of the American Academy of Pediatrics (AAP) guidelines for ADHD diagnosis and treatment in pediatric settings (Leslie, Weckerly, Plemmons, Landsverk, & Eastman, 2004; Leslie et al., 2005; Leslie, Stallone, Weckerly, McDaniel, & Monn, 2006). The primary care practice partners included in this proposed project are drawn directly from Dr. Leslie’s work with these two projects and her connections to the San Diego pediatric community. In Year 01 of the grant, Dr. Leslie will be available for substantial consultation on project set-up via phone and through an in-person trip to San Diego. In the remaining years of the project, she will participate in monthly phone conferences and HSI meetings and will be available for additional consultation, as needed. Furthermore, pilot data collection has begun at a “champion” site within each of the San Diego practice organizations affiliated with this proposal. Please see Letters of Support from the Neighborhood Healthcare (Dr. Nathan McFarland) and Kaiser (Dr. Barbara Lounsbury) project liaisons describing the success of this effort in piloting case identification, clinical record-keeping, space sharing, and assessment and treatment procedures.

In Pittsburgh, project practices are drawn from a PBRN supported by Clinical and Translational Science Institute (CTSI) of the University of Pittsburgh (UL1RR024153). This PBRN served as the recruitment network for the pilot test of the intervention model, and we plan to utilize the same recruitment and assessment procedures that were successful in this feasibility study. The CTSI also supports core PBRN personnel, including liaisons to practices, and we will be able to make use of this experienced research staff in this project.

**Identification of a sample for the proposed project.** In preparation for this proposal, the Pittsburgh team analyzed data from a PBRN screening study (Campo, PI; Brent, co-I) to optimize study entry criteria. Between March 2003 and April 2004, 2,367 families presenting for well child or minor illness visits were approached in primary care waiting rooms. Consenting participants were administered a demographic questionnaire and short screening measures, including the 5-item Screen for Child Anxiety and Related Disorders (SCARED-5, Birmaher et al., 1999), Short Mood and Feeling Questionnaire (SMFQ; Angold, Costello, Angold, & Pickles, 1995), Pediatric Symptom Checklist (PSC-17), and a one-item prompt asking parents if they were worried that their child was anxious or depressed. The first 30 youths from each practice who screened positive for internalizing symptoms on any measure were invited to a follow-up assessment at a second baseline and 6-month follow-up. Overall, 11% of youth in the waiting room screened positive for internalizing symptoms, and 55% of these met diagnostic criteria for anxiety or depression, results comparable to national data. Although both anxiety and depression were common, diagnoses of anxiety were more prevalent (89%) than depression (37%). As would be expected (see Warner, Mufson, & Weissman, 1995), anxiety symptoms were higher in younger (below age 13) youth and depression symptoms more prominent in older (above age 11) youth. Furthermore, fewer late teens (above age 16) chose to participate in waiting room screening. Taken together, these data helped guide our decision to (a) focus on both anxiety and depression in this setting, (b) narrow the age range from our Preliminary Study to exclude youths over age 16, and (c) investigate the moderating effect of diagnosable depression on outcome, given that anxiety seemed a likely common denominator for all youths identified and enrolled.

4.5. Other Work by Investigators and Consultants

Across sites, the investigators and consultants bring together experience with CBT for internalizing youth (Brent, Weersing), mental health services research (Lynch, Weersing, Hoagwood, Miranda), health disparities and ethnic minority mental health (Miranda), clinical trials (Brent, Weersing, Lynch, Miranda, Hoagwood), mental health services in medical settings (Leslie, Weersing, Lynch, Miranda), health economics (Lynch), and...
5. RESEARCH DESIGN AND METHODS

5.1. Overview and Timeline

Over a five year period, we aim to recruit and randomize 210 internalizing youths drawn from two cities and eight primary care practices. We plan to accomplish this goal on the following timeline (codes follow).

<table>
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<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
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A. Project start-up and staff training (Month 0 to 4). In the first four months, we will form our cross-site coordinating committees (Project Management [PM], Data Management [DM], Intervention Delivery [ID]) and begin our weekly call schedule. We also will hire staff and anticipate benefiting from experienced individuals with longstanding relationships to the project and PIs at each site (see Budget Justification; note that we have identified individuals at each site who match our participants in ethnicity, culture, and language). The San Diego team will travel to Pittsburgh to conduct therapist training and to be trained by the Pittsburgh data team in the assessment protocol. We will finalize procedures with sites and purchase equipment and supplies. We will convene our Health Service Implementation (HSI) committee (Lynch, chair) and begin monthly conference calls to problem-solve primary care implementation issues as we begin recruitment. Drs. Miranda and Hoagwood will join the HSI call in Year 01 to consult on issues in project start-up and, in particular, to assist with the successful recruitment, enrollment, and retention of ethnic minority youths.

B. Recruitment (Month 5 to 46). We plan to actively recruit participants for 3.5 years (42 months) of the project. As described in detail in the Recruitment Flowchart (Figure 2), this window is based on experience from our Preliminary Study, estimates of disorder prevalence from analyses of PBRN data, and visit information provided by practices. We have employed a conservative internalizing disorders “hit rate” (10%) and consent rate, and we view this conservative approach as a wise strategy given our efforts to enroll an ethnically diverse sample from a wider range of practices than were employed in our pilot investigation. During the recruitment period, the Project Coordinators (PCs) will have monthly in-person meetings at participating practices to seek feedback on project implementation. PIs will join these clinical practice meetings at least once a year (more frequently in Year 01) and attend additional meetings with practice administrators and governing boards, as required. Sharing practice feedback and monitoring progress toward recruitment goals will be standing agenda items on the weekly PM call.

C. Intervention (Month 5 to 50). During the intervention phase of the project, youths in the BCBT arm will be seen for a maximum of 12 sessions (over 16 weeks). Youths randomized to SMHC referral will be tracked, with clinical monitoring for changes in status. The ID committee will monitor BCBT implementation and coordinate adherence ratings between San Diego and Pittsburgh in Years 02, 03, and 04, to prevent drift.

D. Assessments (Month 5 to 54). Baseline assessments will begin at the same time as recruitment and will continue for eight months following the end of active recruitment, to allow for clinical follow-up assessments at Week 32. Reliability ratings will be collected on an ongoing basis, and assessment quality and progress reviewed on the weekly DM conference call.

E. Data analysis and interpretation (Month 54 to 60). In the final six months of the grant, we will engage in data screening and analysis, interpretation of results, and production of papers. The focus of the HSI committee will shift from implementation to cost-effectiveness analysis, in collaboration with the DM team.

5.2. Participant Entry Criteria

**Inclusion criteria.** We will include youths with **clinically significant anxiety and/or depression**; namely, youths who at baseline meet full or probable diagnostic criteria for Separation Anxiety Disorder, Generalized Anxiety Disorder, Social Phobia, Major Depression (MDD), or Dysthymic Disorder. We also will include youths who meet criteria for the provisional Minor Depression diagnosis, given evidence that subthreshold depression predicts poor functioning and future MDD onset (González-Tejera et al., 2005). We will enroll **school age children and young teens** (ages 8.0 to 15.9 at baseline) **who live with a legal, consenting guardian**.

**Exclusion criteria.** To enhance generalizability, we will keep our criteria to a minimum, excluding only...
those youths who: (a) require treatment other than BCBT, namely youths with bipolar disorder, psychosis, active suicidal ideation with plan, PTSD, substance dependence, current physical or sexual abuse, or mental retardation; (b) suffer from serious or unstable physical illness (e.g., uncontrolled diabetes); or (c) are currently in an active, alternate intervention for anxiety or depression (e.g., antidepressant use).

**Primary language.** We considered several different language inclusion and exclusion criteria. Our final decision was shaped by competing needs: (a) desire to be welcoming to Hispanic, Spanish-speaking families and encourage broad inclusion of Latino/a(s) in our San Diego-based recruitment, (b) need for accurate assessment of participants, given that many standardized measures have only been normed in English versions, and (c) limited capacity to provide parallel English- and Spanish-language supervision for assessments and therapy, particularly within the constraints of an initial efficacy trial. To balance these demands, we plan to include youths and parents are willing to complete study assessments in English. However, we intend to hire bilingual / bicultural IEs and therapists who are able to “code shift” between English and Spanish to facilitate communication with youth and parents who may find themselves more comfortable using Spanish words for emotions in the midst of assessments or therapy. We intend for the bulk of therapy sessions to occur in English, and adherence will be rated on English-language session interactions. This hybrid option appeared to be a useful first step toward demonstrating the cultural competence of the intervention and a good local match to the linguistic needs of our population in San Diego, as 77% of Hispanics in San Diego County self-identify as fluent or good English-speakers (U.S. Census, 2009). If our recruited sample differs substantially from this profile, the HSI will work with our consultant, Dr. Jeanne Miranda, and with the SDSU M-RISP network to appropriately revise our procedures to serve the needs of our participants.

**Concomitant medications.** Youth otherwise meeting study entry criteria who are receiving treatment for a stable medical or psychiatric condition may be included providing that medical management has been ongoing and stable for at least 4 weeks (e.g., stable dose of stimulant medication for ADHD) or if medication has been discontinued for at least 1 week. Youths taking SSRIs or other antidepressant medication will be excluded. BCBT participants will not be administered new antidepressant medications during the 16-week treatment phase within the protocol, but those judged in clinical need of such intervention will be withdrawn from the formal study and provided referral to appropriate services (see Section 5.6.3 for additional detail).

### 5.3. Sample Recruitment, Consent, and Randomization

**Target sample.** We plan to recruit 210 youths, 105 per site (San Diego and Pittsburgh) in the 42 month active recruitment phase of the project. This translates into a recruitment of 5 youths per month across all practices, a rate of recruitment more conservative than our experience in our Preliminary Study. As can be seen in our Recruitment Flowchart (Figure 2), we have adopted a 10% “hit rate” for internalizing disorder for our recruitment estimates. Some teams report very high (35%; Chavira et al., 2004) rates of internalizing disorders in primary care samples; we have based our hit rate on the lowest rate found in our Pittsburgh-based screening studies (see Preliminary Studies). We view this conservative approach as a wise strategy given our efforts to enroll a diverse sample from a wider range of practices than were employed in our pilot investigation.

**Minority recruitment.** Special efforts will be made to recruit and retain eligible Hispanic, African-American, and other minority participants. At both sites, the investigators have worked to develop relationships with primary care practices focused on serving diverse families. In San Diego, we have built a collaboration with Neighborhood Healthcare (NH), a non-profit community health organization that serves low-income patients (73% of patients below federal poverty line) and a large number (42%) of Hispanic families. Similarly, in Pittsburgh, we have developed a relationship with Children’s Community Pediatrics-Pittsburgh Pediatrics and the Children’s Hospital of Pittsburgh Primary Care Center, which serve a high proportion (40% and 71%, respectively) of African-American families. By employing a collaborative R01 mechanism, we will be able to enroll a much more diverse sample of participants across these various practice sites than would be available at either city alone. In San Diego, we anticipate a sample that is (a) 60-70% female, based on prior research with pediatric anxiety and depression, and (b) 60% Caucasian, 30% Hispanic, and 10% other. We also anticipate that Pittsburgh participants will be largely female (60-70%) and Caucasian (60%) or African-American (40%). We will make every effort to reach the goal of equal ethnic minority representation; however, we recognize the challenges in recruiting minority families, and our estimate of 35%, across sites, reflects our appreciation of these difficulties. See Targeted Enrollment page(s) for additional detail.

**Referral.** Our primary recruitment method will be referral from PCCs at the practice sites. For patients who indicate interest in participation, the referring provider will obtain verbal assent to transfer the patient’s contact information to the Project Coordinator (PC). It will be the responsibility of the referring clinician to document assent to be contacted. As an additional referral route, we will post flyers in practice waiting rooms...
describing the project and listing a number to self-refer to the research study. These methods were used in our Preliminary Study and led to 1.5 youths enrolled per practice per month (double our target rate for this project). If PCC referral is insufficient, we will employ screening at all appointments for youth within our target age range (see Section 4.4 for PRBN experience with screening). We also have the option to expand beyond the base of four practices per location. The practices included in this proposal were selected to balance sample diversity, practice diversity (e.g., community clinic versus private office) and on the basis of prior, successful interaction with research projects. Twelve additional practices at 20 locations in Pittsburgh are associated with the PBRN, and Dr. Leslie’s ongoing San Diego-based C3 program is currently based in over 25 primary care locations. These sites are potential recruitment centers, in case of difficulties at our primary recruitment locations. Recruitment challenges will be brought to the HSI committee, and quality of practice relationships will be a standing agenda item on the conference call.

**Consent and enrollment.** Parents of referred youths will be contacted by the PC, who will (a) describe study purpose and procedures, (b) ask a brief set of eligibility questions (e.g., youth is the correct age), and (c) schedule a baseline assessment interview with the PC. At the baseline interview, the PC will seek written consent for participation from parents and assent from youths. Following consent/assent, the PC will conduct the baseline interview to confirm eligibility (see next section on Assessments). Cases will be triaged on the weekly PM conference call with the PIs and PCs to confirm eligibility or exclude youths from the protocol.

**Randomization.** If participants consent and meet entry criteria, they will be enrolled and randomly assigned to BCBT in the primary care practice or referral to SMHC. We plan to balance within each site on minority status, presence of diagnosable depression in the youth, and developmental level (school age [8.0-11.9] vs. teenage [12.0-15.9]) using a modification of Efron’s biased coin toss procedure (Begg & Iglewicz, 1980; Efron, 1971). Youth randomized to BCBT will be contacted by the therapist assigned to their primary care practice, and SMHC families will be provided enhanced referral by the PC. Referring PCCs will receive notification of participant randomization status as well as a brief summary of baseline assessment findings.

5.4. Practice Sites and Providers

**Primary care practices.** We plan to base this investigation in eight primary care practices, four in San Diego and four in Pittsburgh. Information on patient flow, by site, is provided in the Recruitment Flowchart.

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**Figure 2. Recruitment Flowchart**

**San Diego**
- NH Lakeside
  - 15,534 annual visits
  - 890 youths in age range
  - 5,199 youths seen per year
  - 519 internalizing youths 10% hit rate
  - 78 referred 15% hit rate

**Kaiser CM**
- 24,000 annual visits
- 1,550 youths in age range
- 2,826 internalizing youths 10% hit rate
- 273 available in window

**Kaiser OM**
- 26,000 annual visits
- 1,640 youths in age range
- 2,826 internalizing youths 10% hit rate
- 989 available in window

**CCP Armstrong**
- 7,016 annual visits
- 4,706 youths in age range
- 2,826 internalizing youths 10% hit rate

**CCP Natrona Heights**
- 30,680 annual visits
- 4,062 youths in age range
- 2,826 internalizing youths 10% hit rate

**CCP PGH Peds**
- 33,000 annual visits
- 15,000 youths in age range
- 2,826 internalizing youths 10% hit rate

**CH Primary Care**
- 20,000 annual visits
- 4,500 youths in age range

**Pittsburgh**
- NH El Cajon
  - 21,999 annual visits
  - 1,119 youths in age range
  - 28,268 youths seen per year
  - 2,826 internalizing youths 10% hit rate

- NH El Cajon
  - 21,999 annual visits
  - 1,119 youths in age range
  - 28,268 youths seen per year
  - 2,826 internalizing youths 10% hit rate

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- CCP PGH Peds
  - 33,000 annual visits
  - 15,000 youths in age range
  - 2,826 internalizing youths 10% hit rate

- CH Primary Care
  - 20,000 annual visits
  - 4,500 youths in age range
5.5. Measures and Schedule of Assessments

As seen in Table 1, youths will be assessed on three major occasions: (a) Week 0, pre-treatment baseline

BCBT therapists, training, supervision, and adherence. Through this study, we hope to establish the effectiveness of an intervention that is amenable to delivery by typical, community providers. In our Preliminary Study, similar manuals and materials were delivered by a Master’s-level social work therapist and a nurse practitioner. In order to facilitate the eventual dissemination of the protocol, we aim to train therapists in this study with a similar background – community clinicians, with familiarity and comfort with mental health interventions, but not possessing advanced training in CBT or a doctorate in clinical psychology.

We have calculated our budget to reflect a therapist hourly rate per enrolled participant. This will allow us the flexibility to hire several part-time therapists, if needed, to ensure flexible scheduling across practice locations. At least one San Diego therapist will be bilingual and bicultural, and we will seek to hire at least one African-American therapist at the Pittsburgh site. As piloted in our Preliminary Study, therapists will be trained by the treatment developer (Weersing) in two, half-day workshops (see Appendix; Weersing et al., 2008; for a more detailed description). The therapy manual will be reviewed, sample tasks (e.g., setting the agenda) completed, and sessions role played. Following didactic training, Dr. Weersing will provide hands-on clinical training by reviewing all sessions of the first three cases for each therapist. After completion of this intensive training phase, Dr. Weersing will listen to the first session for each youth as well as any sessions requested by therapists for supervision purposes. Continuing clinical supervision will occur weekly, one hour / therapist, throughout the project, and therapist tapes will be randomly sampled for quality assurance ratings (as below).

Overall quality of BCBT implementation will be monitored by the cross-site Intervention Delivery (ID) committee. During the intervention phase of the project (see Timeline 5.1), the ID committee will convene in a weekly conference call to review practical issues in BCBT implementation (e.g., access to space), allow therapists across sites to share clinical wisdom in protocol implementation, and to coordinate treatment adherence ratings in Year 02, 03, and Year 04 of the project. Treatment adherence will be rated by Dr. Weersing and by an independent, expert CBT therapist at the Pittsburgh site (Ms. Kim Poling, senior CBT supervisor for Pittsburgh clinical trials). BCBT therapy sessions will be digitally recorded and 10% will be randomly sampled and rated to determine compliance with the protocol, using a scale that incorporates items closely descriptive of the content of the BCBT manual (e.g., “Did the therapist teach relaxation?”) and global assessments of therapist skillful implementation of the protocol (e.g., “To what extent did the therapist encourage the youth to generate their own examples of treatment concepts?”).
5.5.1. Reliability and quality of assessments
Baseline eligibility interviews will be conducted by Project Coordinators (PCs), who will also be responsible for obtaining consent and assent. Follow-up interviews will be conducted by Independent Evaluators (IE) blind to participant randomization status. Follow-up interviews will be administered over the telephone to aid in subject retention, enhance generalizability of our procedures to community implementation, and allow for cost-effective use of staff time (e.g., reducing travel to practices). We plan to cluster all follow-up IE staff at the San Diego site. Clustering interviewers at a single site may increase reliability and allow for more efficient scheduling. Furthermore, we anticipate that the majority of families will choose to schedule their assessments in the evening, and San Diego’s location in the Pacific time zone will facilitate evening calls in Pittsburgh.

PCs and IEs will be Master’s-level clinicians who have experience in conducting structured interviews using standardized diagnostic and psychosocial assessment tools. Specific training on the project assessment battery and crisis management procedures will be provided to all IEs and PCs in Year 01 in a meeting in Pittsburgh. To be certified, each IE will be required to show percent agreement greater than 80% on five training tapes. Over the course of the study, a random 10% of interview recordings for each IE will be sampled and cross-rated to establish project inter-rater reliability. As discussed previously, all decisions of case inclusion/exclusion will be reviewed by the site PIs and PCs in the weekly PM conference call. General assessment reliability and data management across sites will be coordinated through the DM conference call.

5.5.2. Measurement of demographic characteristics
**General Information Sheet (GIS)** was developed by the investigators and includes age, ethnicity, gender, school placement, and parental education, employment status, and income. Addresses and telephone numbers of three relatives will be requested to be used for locating participants. The GIS will be professionally translated into Spanish at the San Diego site.

**Self-Rating Scale for Pubertal Development** (PDS; Carskadon & Acebo, 1993) is an adaptation of the interview-based Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988). The PDS is a youth self-report designed to be a non-invasive measure of pubertal status without pictorial representations or interviews. It has shown strong correlation with pediatrician-rated and parent-rated pubertal development, and has been effectively used in school settings.

**Multigroup Ethnic Identity Measure** (MEIM; Phinney, 1992) is a 15-item measure developed for use with adolescents and young adults from diverse ethnic groups. The MEIM is designed to measure (a) ethnic identity search and (b) affirmation, belonging, and commitment to one’s group. Item scores are averaged to produce a total score of ethnic identity and may be used to calculate sub-scores. The scale has been validated in young adolescents and has shown consistent reliability across ethnic groups. Investigators have successfully used the scale with youths as young as age 8 (e.g., Reese, Vera, & Paikoff, 1998). The MEIM will allow us to assess ethnic identity beyond simply asking youth to self-identify their ethnic group. The MEIM is available in Spanish.

5.5.3. Measurement of primary clinical outcomes
**Clinical Global Impression Scale** (CGI; Guy, 1976) will be used to assess overall global severity (CGI-S) and improvement (CGI-I). The CGI is traditionally a clinician-completed measure, and we will have our IE (blind to treatment assignment) complete ratings at each in-person interview. CGI-I scores of 1 (“very much improved”) or 2 (“much improved”) indicate an acceptable treatment response. The CGI-I will be the overall, global outcome measure for the project. The CGI is not available in Spanish; however, it is rated by the IE on the basis of the K-SADS (see below) and does not require additional prompts.

**Pediatric Anxiety Rating Scale** (PARS; RUPP, 2002) is a clinician-rated measure of anxiety comprised of a 50-item symptom checklist and 7 global severity/impairment items. The PARS has high interrater reliability, adequate internal consistency, and fair test-retest reliability. There is support for convergent and divergent validity and sensitivity to treatment effects in previously conducted clinical trials. The PARS will be the primary outcome measure of anxiety.

**Children’s Depression Rating Scale – Revised** (CDRS-R; Poznanski & Mokros, 1996) is a clinician-rated measure of depression that integrates youth and parent report to assess the presence and severity of depression in youths. The CDRS-R is composed of 17 items tapping the major features of depression; scores
of 40 and above are considered reflective of a depressive diagnosis. The CDRS-R has good interrater reliability, internal consistency, and convergent validity with other measures of youth depression, and is sensitive to treatment effects. *The CDRS-R will be the primary outcome measure of depression.*

5.5.4. Measurement of psychopathology, satisfaction, and impairment

**Schedule for Affective Disorders and Schizophrenia for School-Age Children** (KSADS; Chambers, 1985) is a semi-structured interview designed to ascertain psychiatric illness according to DSM-IV criteria. Probes and objective criteria are provided to rate individual symptoms. Interrater and test-retest reliability have been established, as well as convergent and discriminant validity (Kaufman, Birmaher, Brent, & Rao, 1997). The KSADS will be administered at baseline to assess for inclusion/exclusion into the study. To ease participant burden, only the anxiety and mood modules will be administered at follow-up assessments. *This measure is available in Spanish, translated for use in a Mexican population (Ulloa et al., 2006).*

**Screen for Child Anxiety Related Emotional Disorders** (SCARED; Birmaher et al., 1999) is a 41-item measure of anxiety symptoms with youth- (SCARED-C) and parent-report (SCARED-P) versions. The SCARED is designed to screen for the presence of DSM-IV anxiety disorders in children and adolescents and produces a total score and subscores corresponding to DSM anxiety clusters. The scale has been validated in diverse clinical and community samples, with good interrater and test-retest reliability, as well as convergent and discriminant validity (Kaufman, Birmaher, Brent, & Rao, 1997). The SCARED will enable us to examine the impact of the intervention on youth versus parent perceptions of anxious symptomatology and to collect symptom data at interim assessments. *This measure is not yet available in Spanish; however, the San Diego research group has been working to develop a Spanish-language version of the SCARED (Gonzalez, Weersing, et al., 2009).*

**Mood and Feelings Questionnaire** (MFQ; Wood, Harrington, & Moore, 1995) is a 34-item self- and parent-report inventory of depressive symptomatology in children and adolescents with sound psychometric properties and good sensitivity to symptomatic change over time. As with the SCARED, we have experience successfully administering and analyzing short forms of the MFQ as a primary care screening instrument. The MFQ will enable us to examine the impact of the intervention on youth versus parent perceptions of depressive symptomatology and to collect symptom data at interim assessments.

**Child Behavior Checklist** (CBCL; Achenbach, 1991) is a 113-item parent-report assessment of child behavioral and emotional problems with published reliability and validity data. The CBCL provides age- and gender-normed total dysfunction, social impairment, externalizing behavior problems, and internalizing symptom scores. We plan to use the total problem score as an index of overall youth dysfunction and to examine the pattern of subscale scores to better understand comorbidity and impairment in the sample. *The CBCL is available in Spanish.*

**Client Satisfaction Questionnaire** (CSQ-8; Atkisson & Greenfield, 1995) is an 8-item measure of satisfaction with services, with good internal consistency. The CSQ will be given to youths and parents. *The CSQ is available in Spanish.*

**Columbia Impairment Scale** (CIS; Bird et al., 1993) is a reliable and valid 13-item questionnaire that evaluates global impairment along 4 areas of dysfunction (interpersonal relations, psychopathology, school function, use of leisure time).

**Health Utilities Index** (HUI; Feeny, Torrance, & Furlong, 1996; Feeny et al., 2002; Feeny, Furlong, Saroj, & Sun, 2004; Furlong, Feeny, Torrance, & Barr, 2001; Torrance et al., 1996) consists of several related

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multi-attribute health status classification systems: the HUI1, HUI2, and the HUI3. The scores from the instruments are preference- or utility-based, on the dead to healthy scale, where death has a score of 0 and full health a score of 1. The HUI2 was developed for use in child research and has been used extensively in studies of children. The HUI will be transformed into Quality Adjusted Life Years (QALYs) and used to provide a cross-disorder index of clinical effectiveness for our CEA analysis. The HUI is available in Spanish.

5.5.5. Measurement of parent psychopathology

Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is a widely used, brief self-report measure of depressive symptoms with sound psychometric properties. We will ask the primary caretaker of youths to complete the BDI in order to assess parental depression for our moderator analyses. The BDI is available in Spanish.

5.5.6. Measurement of service use and cost

Child and Adolescent Services Assessment (CASA; Ascher, Farmer, Burns, & Angold, 1996) measures health service use during a specified period of time (e.g., since last interview) received by the youth. The CASA has been shown to have acceptable reliability and validity (Ascher et al., 1996). We will conduct detailed CASA interviews at baseline, Week 16 and 32; in addition, we will employ a CASA services screen in the Week 8 and Week 24 brief assessments to minimize missing data for the cost-effectiveness analyses (CEA). The detailed data provided by the CASA will be used to conduct the CEA and also will allow us to carefully describe SMHC comparison group services and to examine the types of services used by participants at each site to identify possible differences in service availability between sites. We will document total health service utilization (physical and mental health) and probe for complaint prompting use of services.

Implementation Cost Inventory (ICI) will be developed by the HSI committee to carefully document the cost of set-up activities that would be necessary in order to implement the BCBT protocol in practice. These costs will include time spent training PCCs in case identification and therapists in the BCBT protocol, and we will estimate the cost of periodic retraining (3 year intervals) that would be necessary to maintain fidelity of the model in practice. In addition, start-up supply costs will be estimated (e.g., printing manuals) designed to reflect a one-year “starter kit” version of the program.

Barriers to Treatment Participation Scale (BTPS; Kazdin, Holland, Crowley, & Breton, 1997) is a parent-report interview identifying barriers impacting treatment receipt or delivery. The interview is comprised of five subscales: (a) stressors and obstacles that compete with treatment, (b) treatment demands and issues, (c) perceived relevance of treatment, (d) relationship with the therapist, and (e) critical events. The BTPS has demonstrated high internal consistency and demonstrates predictive validity for client attrition. In addition, items addressing practical barriers to treatment participation will be used as a screen at baseline to aid in SMHC referral for youths (see Section 5.6.2).

Satisfaction Exit Interview (SEI). In Year 01, the HSI committee will develop a set of open-ended interview questions to tap parents’ and youths' experience in the therapy program and suggestions for improving treatment. Given that this project will enroll a more diverse sample of participants than in our Preliminary Study, we plan to ask participants who received BCBT whether the program was (a) “a good fit to your family and how you solve problems”, and (b) “a good fit to your culture and how you see the world.” We also will ask whether the treatment was the correct length, taught useful skills, focused on the right topics, and was a good fit to primary care. The SEI will be the last data collected from families. With support of the M-RISP (San Diego), the HSI committee will develop a Spanish-language version of the interview.

Provider Satisfaction Scale (PSS). As described in Section 5.1, PCs will meet monthly with clinical and administrative staff at each practice to solicit feedback on (a) study procedures and progress and (b) fit of the BCBT program to practice settings and families. To systemize this process, in Year 01, the HSI committee will develop a short survey tapping these domains, based on existing customer satisfaction measures (e.g., “would you recommend this program be adopted by a colleague’s practice?”), perceived barriers to immediate implementation (e.g., difficulties scheduling, sharing space, communicating), and perceived barriers to long-term implementation (e.g., billing, fit to culture of primary care). In addition, there will be room provided for free response comments and suggestions. The survey will be distributed at practice meetings and through secure CTSI web-portal login for staff unable to attend in person. This format (self-report) and frequency (monthly) was suggested by providers, over more time-intensive and infrequent methods, such as annual meetings of focus groups. Data will be used for internal quality control (e.g., quickly solving problems in communication) and to provide pilot data for future, larger-scale investigations of implementation and dissemination.

Therapy Procedures Checklist (TPC; Weersing et al., 2002) is a 50-item therapist-report measure that assesses use of different child therapy techniques. Scales have shown excellent internal consistency and
The last 10 minutes of the session for a brief review of content and assistance in homework completion. In the session, youths are given relaxation practice and mood monitoring as homework. The parent is invited to join (diaphragmatic breathing and progressive muscle relaxation) are taught as a default. At the end of the relaxation tools for practice. If youths do not express a preference, somatic relaxation techniques (formally introduced in Session 4). After this overview, the youth are encouraged to pick one of the three activities (relax your world). Note that the inclusion of relaxing activities is a step toward behavioral activation processes discussed in Session 1). Youths are provided with an overview of three tools for relaxation monitoring as homework. Parental assistance with homework will be sought for school age youths. The goal of the session is to normalize the experience of stress, anxiety, and low mood and to engage the youth and parent in a discussion of how these patterns map on to their current experience. Information from the baseline assessment will be verified and updated. At the end of the session, youths are given mood monitoring as homework. Parental assistance with homework will be sought for school age youths.

**Session 1: Psychoeducation and treatment rationale (substantial parent attendance).** During the first session, the therapist provides psychoeducation on depression and anxiety in youth, focusing on how both types of negative affect are typically a response to stress or threat. Youth and parents are provided information on the fight or flight response and the tendency to withdraw and avoid in the face of threat. The goal of the session is to normalize the experience of stress, anxiety, and low mood and to engage the youth and parent in a discussion of how these patterns map on to their current experience. Information from the baseline assessment will be verified and updated. At the end of the session, youths are given mood monitoring as homework. Parental assistance with homework will be sought for school age youths.

**Session 2: Relaxation and coping with negative affect.** In the second session, the youth is taught relaxation as a tool for lowering physiological arousal and coping with stress (interrupting the negative mood processes discussed in Session 1). Youths are provided with an overview of three tools for relaxation – somatic relaxation (relax your body), guided imagery (relax your mind), and the use of soothing and pleasant activities (relax your world). Note that the inclusion of relaxing activities is a step toward behavioral activation (formally introduced in Session 4). After this overview, the youth are encouraged to pick one of the three relaxation tools for practice. If youths do not express a preference, somatic relaxation techniques (diaphragmatic breathing and progressive muscle relaxation) are taught as a default. At the end of the session, youths are given relaxation practice and mood monitoring as homework. The parent is invited to join the last 10 minutes of the session for a brief review of content and assistance in homework completion.

**Session 3: Problem solving skills training.** Next, we focus on problem solving skills, as a tool for interrupting negative affective spirals and selecting responses that (a) “solve” controllable problems through active engagement (e.g., talking to a teacher about making up a missed test, rather than skipping school), and/or (b) lower physiological arousal and raise positive mood (e.g., visiting your friend next door when your sister is fighting with your parents). In the bulk of the session, youths are prompted to identify several problems that routinely lead to feelings of anxiety and/or depression and to start generating possible ways to either solve or cope with these situations. This activity is in preparation for goal setting in the following session. For home practice, youths will be assigned continued mood monitoring, relaxation, and (if appropriate) trying a strategy identified through the problem solving exercise. Parents are invited for a check-in and assistance in homework completion will be sought, as developmentally appropriate.

**Session 4: Reducing avoidance and setting goals (substantial parent attendance).** Session 4 is designed to set the agenda for the remainder of treatment. To this point, youths have learned skills for coping with the “front end” of negative affect. From this point forward, youths are encouraged to engage in different responses on the “back end” of affect – approach instead of avoidance for dealing with anxiety, and activation instead of withdrawal for dealing with depression. As this is a short-term protocol, youths and parents are encouraged to (a) select practical, attainable goals that (b) they have a high motivation to complete and (c)
seem likely to improve mood. The therapist guides the selection of goals and helps the youth and parent begin constructing a step-by-step plan for achieving goals. For primarily anxious youths, this plan will closely resemble traditional anxiety hierarchies, although it will necessarily be limited by the short-term nature of treatment. For primarily depressed youths, this plan will be quite similar but will focus on graded steps toward achieving activation goals. Anxious-depressed youths will have engagement plans that resemble both of these, namely, plans for activation that are (likely) also graded in the level of anxiety produced by each step. In our Preliminary Study, youth plans tended to center around two main themes (a) increasing developmentally appropriate separation from parents, especially around sleeping and staying home alone, and (b) enhancing engagement with peers. For school age youths, we anticipate that parents will participate for the entire goal setting session. For young teenagers, we plan on engaging in goal setting with the teen for the first half of the session and bringing in the parent for the second half of the session. At the end of the session, youths are assigned continued mood monitoring, relaxation practice, and review of the goals identified in Session 4.

**Session 5-7: Increasing engagement and activation.** Sessions 5-7 are devoted to making incremental progress on activation / exposure plans. Youths are provided with in-session, enactive practice (e.g., exposure to the dark for youths afraid of sleeping alone, role play of conversations for youths wishing to increase their social connections). Significant time is spent reviewing progress out of session, problem solving any obstacles to implementation, and planning for practice for the following week. It may be desirable to space out these sessions to allow youth additional time to practice and implement plans. Homework in this period will be individualized according to youth plans, and parent assistance sought as developmentally appropriate.

**Session 8: Relapse prevention (substantial parent attendance).** In the final session, youths and parents will review the central lessons of treatment, the youth’s specific progress on goals, and plan for future growth. The problem-solving framework will be re-introduced, and youths and parents encouraged to imagine future stressors and to develop coping plans. Based on our experience in the Preliminary Study, we also will ask the caregiver, youth, and therapist to complete a CGI-S rating for discussion in this session. To prevent relapse, for all youths with a CGI-S in at least the mildly ill range (≥3), we will recommend additional treatment booster sessions to continue working on engagement plans and toward treatment goals. Youths whose clinical condition has worsened since baseline will be removed from the protocol and referred to psychiatric services (University of California, San Diego in San Diego; Western Psychiatric Institute and Clinics in Pittsburgh) and their pediatricians for a recommended course of SSRIs, in addition to out-of-protocol psychosocial treatment.

**Session 9-12: Booster sessions.** As discussed in the previous session, youths who are still evidencing impairing symptoms at Session 8 will be encouraged to continue in the BCBT protocol. Families will be provided with up to an additional 4 sessions. These sessions are designed to be used to check-in on symptoms and functioning and provide coaching on the use of skills and continued implementation of plans. We include this element of treatment to enhance the impact of the short treatment protocol and to explore the appropriate “dose” of clinician contact needed to implement the program successfully in our diverse sample.

### 5.6.2. Enhanced Referral to SMHC

**Rationale.** The comparison condition in this proposed project is the most common mental health treatment option in pediatric primary care – referral to specialty mental health care (SMHC). Comparison to SMHC referral will provide a useful public health benchmark for the effects of the BCBT program and will enable us to collect meaningful cost-effectiveness data on SMHC and BCBT. In addition, we view SMHC referral for depressed and anxious youths as a more ethical comparison condition than many other options, such as a no-treatment control, waiting list, or “weak” intervention (e.g., psychoeducation or relaxation alone). Youths referred to SMHC have the universe of potential mental health interventions available to them, and their families are not restricted in their choice of treatments. As such, SMHC referral also serves as a conservative test against a range of potentially active treatments (e.g., SSRIs) and interventions with less compelling empirical support (e.g., nondirective therapy; Brent et al., 1997; Weersing & Weisz, 2002a).

While we view this design as well-justified from a public health perspective, we are sensitive to the critique that enhanced external validity may come at a cost to internal validity. The content and dose of SMHC may be variable, some youths may fail to receive SMHC services, and it could be difficult to draw conclusions on whether the specific techniques provided in BCBT were superior to SMHC. To address these concerns, we have sought to (a) craft an enhanced version of SMHC referral (described below), (b) build collaborations with specific SMHC sites that provide a range of culturally appropriate and geographically convenient services, (c) carefully measure service use (CASA) and treatment content (TPC) in SMHC and BCBT, (d) conduct cost-effectiveness analyses in order to weight our outcome by any differences in service use between arms, and (e) enhance our measurement of barriers to service use (BTPS) to better understand
Enhanced referral model. Youths in the SMHC arm will be provided with enhanced referral to local outpatient services. Our enhanced referral procedures are modeled on evidence-based practices for reducing SMHC no-show rates. Mary McKay and colleagues have developed a 30-minute telephone intervention designed to increase attendance at first appointments in community SMHC. In their work, 86% of families receiving the engagement procedure followed-through with their initial appointment, in comparison only 44% of families randomized to usual phone intake attended a single session of care (McCadam, & Gonzales, 1998). Note that in our Preliminary Study, 97% of youths in BCBT and 59% of youths referred to SMHC attended at least a single appointment – in line with data from the McKay engagement trial.

Key elements of the McKay approach include (1) providing psychoeducation, (2) enhancing the efficacy of help-seekers, (3) exploring previous negative SMHC experiences, and (4) problem-solving practical obstacles to treatment. We have enhanced our SMHC referral procedures to address each of these steps. Following the baseline interview, the PC will contact the family with their SMHC randomization status to begin the process. To address Step 1, the PC will provide feedback to parents on the results of the assessment. We will couple this feedback with information on the course of untreated anxiety and depression, a description of intervention options, and a discussion of the potential positive effects of treatment. To address Step 2, we aim to enhance parent efficacy by making the experience of referral more personal and more concrete. We have developed collaborations with specific SMHC referral sites (see SMHC Letters of Support and description below), and we will provide help-seeking parents with information on what to expect and how to navigate specific SMHC site intake processes. With regard to Step 3, we anticipate than many of our primary care participants may not have previous experience with the mental health system. However, we have developed relationships with both a primary and secondary SMHC referral site for each pediatric practice catchment area to provide families with a choice of providers. Of course, families also are free to seek care from providers not on our referral list. We will seek feedback over the course of the project to ensure that our referral choices are well-accepted by families and additional referral sites may be developed, as needed. To address Step 4, we will draw items from the BTPS to screen all families at baseline (pre-randomization) on practical barriers to attending therapy in either arm of the study. In our SMHC referral call, we will be prepared to provide information on community resources to address barriers to service use (e.g., transportation), and we are developing a resource book for each site with a summary of useful services. We will assist families in problem-solving foreseeable obstacles to care, including new concerns that may have arisen since baseline. As planned previously, at the end of this call, parents will be offered a biweekly follow-up call with the PC to check access to services, provide referral to different agencies in case of difficulties, and assess changes in youth clinical status.

SMHC sites. In preparation for our resubmission, we have worked to build collaborative relationships with primary and secondary SMHC referral sites for each pediatric practice catchment area (see following table). Letters of Support from each SMHC site are provided in the Appendix, with a description of available services. We have sought to develop collaborations with sites that provide services that are (a) geographically-convenient for families from each practice area, (b) culturally appropriate, including bilingual services in San Diego, and (c) free or reduced-cost and/or care provided within pre-paid insurance networks (e.g., Kaiser referrals, see Letter of Support). This SMHC network has been developed in collaboration with pediatricians at each site and these providers have been vetted as preferred referral sources by the practices. We do not view this list as static, and we will seek feedback from families and practices to update our referral system.

<table>
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<th>San Diego</th>
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<td>NH Lakeside</td>
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<td><strong>Secondary</strong></td>
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<td>East County Communities Center (ECCC), San Diego State University Psychology Training Clinic (SDSU), Kaiser Permanente psychiatric services (Kaiser), Family Psychological Services (FPS), Allegheny Mental Health Associates (AMHA), University of Pittsburgh Clinical Psychology center (CPC), Family Services of Western Pennsylvania (FSWP)</td>
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Measurement of service use and CEA. Our collection of the CASA will enable us to document the location of services (private practice, community mental health), type of services received over the course of the study (physical vs. mental health), level of service (outpatient, inpatient, other), and the number of sessions of each type of service received. To gain a better understanding of the content of any psychotherapy provided, we will seek permission to contact outpatient SMHC providers and ask these providers to complete the TPC.
In our analyses of clinical outcomes, we will examine service utilization as a covariate (e.g., comparison of BCBT and SMHC referral trajectories on the CDRS-R, controlling for number of therapy sessions). Furthermore, our cost-effectiveness analysis will explicitly weight the clinical outcomes of BCBT and SMHC referral by the utilization / cost of services associated with each arm (see Section 5.7.4).

5.6.3. Stopping or withdrawal from treatment or the study

In this study, we aim to enroll youths with mild to moderate levels of anxiety and depression, who can be maintained in a brief, primary care-based intervention. Youths requiring a higher level of care at baseline will be excluded from the study and provided with referrals. By design, the sample is not intended to require frequent management of crises; however, we anticipate that such situations may arise. In our pilot study, 4 of the 54 enrolled youths were rated as being “minimally worse” at a follow-up assessment (1 in BCBT, 3 in SMHC referral). Note that no youths were ever rated more negatively than this category.

In the BCBT arm, problem solving skills are introduced early in treatment to assist youths and therapists in managing emergent stressful situations. In a similar fashion, all IEs will be trained in detailed procedures for detecting, triaging, and responding to emergent crises revealed in the assessment interviews. Dr. Brent is an internationally-recognized expert in the study and clinical care of suicidality in youth, and we base our crisis procedures on those developed by his TORDIA team to manage the severely depressed and suicidal sample of adolescent enrolled in that investigation. See the Human Subjects section for additional details.

Youths may be formally withdrawn from the study by the PIs if they develop a condition that meets criteria for exclusion (e.g., psychosis) or if they show evidence of clinical deterioration (CGI-I ≥ 4) during the course of study participation. If a youth is withdrawn from the study, he/she will be provided referral to community resources, including the option of open treatment with his/her referring doctor or outside referral depending on what is judged to be clinically appropriate and matches family preferences. As described in the Human Subjects section, all potential study withdrawals will be discussed in the PM committee, documented, and reported to the study Data Safety and Monitoring Board and site Institutional Review Boards.

5.7. Data Management and Statistical Analysis

5.7.1. Data management

The proposed study will benefit from the Pittsburgh team’s extensive experience serving as data center for multi-site clinical trials. As described previously, the cross-site DM steering committee (Brent, chair; Iyengar, co-chair) will oversee the collection, entry, quality, and analysis of all project data. The HSI committee (Lynch, chair) will coordinate with the DM team for the analysis of cost-effectiveness data.

Data entry and verification. Data from the assessment process will be collected using scannable forms, then scanned, verified, and stored under the supervision of the project DA in Pittsburgh, who will check for missing data or outlying values. These scannable forms have performed well in other clinical trials conducted in Pittsburgh, including in our Preliminary Study. Ten percent of forms will be selected at random by the Data Manager (Ms. Porta) and compared against scanned and entered data as a procedural check. Prompt data entry and checking will help detect missing or aberrant values and ensure overall data quality.

Data storage and security. Data will be entered into a password-protected desktop computer using a project-specific, local Access database. Data from Access can be easily exported to statistical packages, such as SPSS, SAS, and HLM (specialized software for hierarchical random-effects regression analyses), for screening and analysis. Participant names and other identifiers will not be included in the electronic database, and participants will be identified by alphanumeric codes unrelated to known identifiers. Hard copies of data with potential identifiers will be stored in locked file cabinets with access restricted to key study personnel. Systematic data back-up will be performed weekly with CD-ROM disks with extended life expectancy.

5.7.2. General analytic strategy

We will use a variety of statistical methods to address the primary and secondary aims of this study. We will test our main hypotheses first using the most parsimonious model (chi-square for categorical outcomes or t-test or the non-parametric Mann-Whitney test for continuous outcome). We then move to hierarchical linear modeling (HLM) with several covariates, for which we will check our candidate models using regression diagnostics (e.g., plots of residuals and deviances). For our secondary analyses, we will use model selection procedures such as Akaike Information Criterion (AIC) and changes in log-likelihood to find the best predictors of the outcomes of interest. Sensitivity analysis (analyzing the data using different approaches) will be utilized, and a finding will be considered robust if it is quantitatively similar across different approaches.

Intent to treat strategy. All treatment dropouts and subjects withdrawn from the study will be encouraged
to continue participating in study assessments, in order to allow for intent to treat (ITT) analysis of primary outcomes (Lavori & Dawson, 2001). In ITT, outcomes are analyzed by randomized status, without regard to subject adherence to protocol. ITT analyses are designed to (a) provide the fairest “public health test” of an intervention’s effects, by including real world non-adherence within the estimates of outcome; and (b) preserve the randomized design of clinical trials, a feature that is corrupted by following only study completers.

**Plan for missing data.** In addition, we will treat both BCBT dropout and study dropout as outcomes for analysis (with chi-square and survival analyses). We will characterize dropouts carefully, recording reasons for dropout and symptoms at time of dropout, and we will perform analyses to characterize subjects who leave the study prematurely. Missing data are problematic because we generally do not know the true reasons for missingness but have enough information to make judgments about which reasons are plausible and which are less so. Therefore, our general approach is to conduct a sensitivity analysis: In short, we use different methods of imputation and arrive at our conclusions based on the results and our assessment of the missingness mechanisms. Such an approach is now feasible because of software (e.g., SAS, STATA) that contains the necessary programs for complete analysis, LOCF, and multiple imputation. If, however, we suspect that the missingness is informative (that is, not Missing At Random), we will write programs to address biases using weighted distributions. We have written such programs in studies of maximum likelihood estimation based on selection models (Iyengar & Zhao, 1994; Iyengar, Kvam, & Singh, 1999).

**Data screening and inclusion of moderators and covariates.** We will begin by screening data to check for outliers and missing data patterns, using histograms and scatterplots. We will then use univariate methods to examine the relationship between the main outcomes (CGI, PARS, CDRS-R), our a priori moderators (youth depression, maternal depression, site), and other potential covariates such as age, minority status, gender, and pediatric practice within site (e.g., KP versus NH, within San Diego). We will explicitly examine service utilization as a potential covariate (e.g., effects of BCBT vs. SMHC, controlling number of therapy sessions).

In these preliminary analyses, we will assess for independence of predictors – for example, we suspect that youth depression status may be collinear with age and gender (i.e., rates of depression may be higher in adolescent girls). We chose our a priori moderators with these natural correlations in mind and selected those variables with the strongest theoretical impact on treatment outcome (e.g., choosing depression status over developmental level). However, if there is sufficient independence between our planned moderators and these other demographic variables, we will investigate their value as additional, exploratory covariates. In particular, we plan to probe age as a continuous variable, age coded as developmental level, and youth-report of pubertal status to determine if they are sufficiently distinct from our a priori moderators to include in analyses. We will also test whether there is substantial collinearity between our a priori moderators (e.g., youth depression and maternal depression at baseline). To resolve these dependencies in the data, we will use regression-based and signal detection methods of variable selection to determine which variables to enter in our analytic models first, and we will assess the impact of each moderator in a stepwise fashion. This hierarchical approach has been used successfully in randomized trials (e.g., Owens et al., 2003).

We will include exploratory covariates as control variables that are significant at level $p = 0.10$ in later analytic models, either by stratifying on the particular variable, covarying the factor, or testing for outcome x variable interactions. **All analyses will include site as a covariate.** If site heterogeneity is present, we will seek to ascertain the causes (e.g., differences in participant populations) that might have led to outcome differences. Since primary care practices are nested within site, there is potential for additional practice effects within site (cf., no such effects were found in the Preliminary Study). Random effects will be used to model within-practice correlation; we expect that this approach will have negligible effect on power as it adds only one additional parameter to analytic models and thus reduces the residual degrees of freedom by one.

**5.7.3. Analysis of primary aims**

**Clinical effectiveness (Aim 1).** Clinical effectiveness of the protocol will be assessed in three domains: IE-rated global clinical improvement on the CGI-I (dichotomous judgment, CGI $\leq 2$), anxiety on the PARS, and depression on the CDRS-R. IE ratings on the CGI-I will serve as the primary outcome of the trial. **We hypothesize that BCBT will be superior to SMHC referral across domains (global improvement, anxiety, and depression) at Week 16 and Week 32 follow-up.** We will use chi-square and logistic regression procedures to test for differences between BCBT and SMHC referral in the proportion of youths achieving significant improvement (CGI-I). To assess the effects of the intervention on continuous outcomes, random-effects regression will be used across Week 0 to 32, with significant differences in symptom slope (i.e., treatment x time interaction) indicating a treatment effect. Note that data may be transformed (e.g., log-time), if necessary, to allow for linear modeling of effects. For our random regression models, we will begin with
assuming a low-order autoregressive dependence structure (e.g., AR[1]) for measurements over time. We will check the fit of this model using autocorrelation and partial autocorrelation functions of the residuals and make adjustments if the initial assumptions of our starting model are not adequate. In this process, we will examine slope coefficients and other model parameters to see how they change with different assumptions about the variance-covariance structure (i.e., a sensitivity approach).

We expect that our primary outcome (CGI-I) and our continuous measures are likely to be correlated, and we will study the nature of this relationship using graphical (e.g., to judge the linearity or non-linearity of relationship) and numeric methods (e.g., Pearson correlations, principal components analysis). However, while related, these three measures tap unique domains of outcome—overall improvement and functioning, specific depression symptoms, specific anxiety symptoms—and different time points (CGI-I references improvement from baseline; PARS and CDRS-R reflect recent symptoms at the time of assessment). Furthermore, youths may have different patterns of comorbidity across the anxiety disorders and depression, and we do not expect that these measures will be so correlated as to represent a single severity index.

**Treatment response and moderation (Aim 2).** In addition to testing for significant mean effects of treatment, we plan to examine the individual trajectories of participants and model variability in response—an important indicator of the strength of the intervention and the range of outcomes that could be observed in future research. Our analytic strategy will build on the techniques described in Aim 1—logistic regression procedures for global clinical improvement and random-effects regression models for anxiety and depression outcomes. We will estimate the proportion of between-subject variance accounted for by treatment (i.e., results of the Aim 1 analyses) and test whether significant additional between-subject variance remains (i.e., does treatment account for all non-random differences in observed outcomes?). **A priori, we plan to assess if youth level of depression symptoms and maternal depression appear to account for significant variability in outcome.** As an exploratory analysis, we also plan to examine the effects of ethnicity, defined in terms of the predominant ethnic groups for San Diego (Caucasian and Hispanic) and Pittsburgh (Caucasian and African-American), within each site, controlling for differences in SES/income. Additional exploratory covariates will be included in analyses, as described in the Data Screening section above. **On theoretical grounds, we will prioritize inclusion of age as a covariate, if statistical methods alone do not strongly contraindicate inclusion in the model.**

**Power to detect effects.** There is one primary outcome: clinical global improvement defined as CGI ≤ 2, assessed at Week 16 and Week 32 (Bonferroni-corrected α = 0.025). The most basic analysis of this outcome will involve the comparison of proportions using a chi-square analysis. In addition, logistic regression will be used when additional covariates are warranted (see Data Screening section above). With a sample size of 105 per group, we are able to detect an effect size of approximately 0.42, which is a 21% expected difference in improvement rate between BCBT and SMHC, with a power of 0.80. Note that in the test of our draft materials (see Preliminary Studies), the CGI-I effect size was substantial (42% difference in improvement rate), and we found significant effects with only 60 participants. This is an initial parameter estimate, but it provides some evidence that we will be adequately powered to assess our primary aim of clinical effectiveness.

For our moderator analyses of the CGI, we conducted simulations based on MacKinnon, Lockwood, Hoffman, West, and Sheets (2002). Including our three a priori moderators (youth depression, maternal depression, and site), we anticipate power (> 0.80) to detect medium (0.46) effects. **Should our data screening procedures suggest the need to test an additional, fourth moderator (e.g., age, pubertal status, or developmental level), power would still be adequate to detect medium effects (0.50).** For our regression analyses of the CDRS-R and PARS, with up to three a priori moderators (youth depression, maternal depression, and site), up to three exploratory covariates, all of their two-way interactions, and up to ten three-way interaction terms, we will have 190 degrees of freedom for the error term; thus, we expect to have power to detect an effect size of 0.30 with power of 0.80.

As discussed previously, we will adopt an ITT approach to analysis and to follow all youths in our assessment protocol, regardless of treatment dropout or non-adherence. With this strategy, we anticipate that study attrition will be minimal. However, if 15% of the sample was lost to follow-up, analyses of our primary aims would still be sufficiently powered to test our hypotheses. In this scenario, we would be powered (0.80) to detect at 24% difference in response between groups, an effect size of 0.34 in our regression models, and effect size of 0.48 for our planned moderator analyses.

**5.7.4. Analysis of secondary aim (cost-effectiveness)**

We are developing this intervention close to the eventual service site for its dissemination, and we will be attending to real world feasibility issues throughout our research program. **The decision to adopt a new**
Experts have noted that there are numerous challenges to accurately estimating incremental CE ratios (Gold, Siegel, Russell, & Weinstein, 1996). We next describe our procedures for assessing each component of the ratio, namely, the CE clinical metric and the costs of the BCBT intervention and other health services.

Clinical metrics. Youth in this investigation may be suffering from significant depression, anxiety, or both. To capture this clinical diversity, we will calculate CE ratios using four different clinical metrics, namely, cost per: (a) depression-free-day (DFD), (b) anxiety-free-day (AFD), (c) psychopathology-free-day (PFD), and (d) increase in health utility. We will calculate DFDs using normative data from our depression outcome measure, the Children's Depression Rating Scale (CDRS-R). Using weights established empirically in the TORDIA study, each day will be assigned a DFD value between 0 (depression free) and 1 (clinically depressed), with proportional DFD values assigned for subsyndromal days. We will conduct sensitivity analyses to probe the validity of our CDRS-R cutoff values in this sample. Total DFDs will be calculated by adding estimated daily DFD values over the eight-month study period. We will adopt a similar procedure to calculate AFDs, using normative data from the Pediatric Anxiety Rating Scale (PARS). PFDs will be calculated as a mean composite across DFDs and AFDs, and, similarly, we also will explore cost-effectiveness across both disorders by using QALY scores from the Health Utilities Index (HUI2; HUI3). This utility-based approach has been used in studies of the cost-effectiveness of adult depression treatments (Sherbourne et al., 2001) and will allow us to benchmark our results against the more developed adult primary care treatment literature.

Overall approach to measurement of cost. In our analysis, costs will be assessed with the following general strategy: (a) calculate direct costs of BCBT intervention (labor, equipment, supplies, facilities, management); (b) calculate total other health care use and expense for each participant, in both arms of the study (BCBT and SMHC referral); and (c) as described previously, evaluate the cost-effectiveness of BCBT for
producing improvements in anxiety/depression from the perspective of the HCO (Udvarhelyi, Colditz, & Epstein, 1992). Note that this approach includes all billable health care services as “costs” for youths in BCBT, not simply the cost of the intervention program itself. This methodology will allow us to capture any cost-offset of participation in the BCBT program or, conversely, any increase in costs associated with additional service utilization by youths in the BCBT arm. This same strategy will be used for determining costs of the SMHC arm, namely, counting all health service utilization as a cost associated with SMHC referral.

**Measurement of direct BCBT intervention costs.** An intervention “input” will be defined as any service provided to the BCBT intervention group that is not provided to the SMHC control group by the research team. We will not include research-specific inputs on either side of this calculation, such as IE time spent conducting baseline assessments. The direct costs of the BCBT intervention program are the salary and fringe benefits for labor inputs (e.g., therapists, appointments clerks), costs of medical office space to conduct the intervention meetings, costs of treatment manuals and materials and therapy supplies, and general administration and overhead. Purchased inputs (e.g., manual printing) will be valued at their invoiced cost. Professional labor inputs will be valued using unit cost estimates developed from a national database (see costing algorithm).

**Measurement of utilization of health care services (Total HCO Costs).** Comprehensive medical care utilization profiles will be developed on every participant. The CASA collects comprehensive data on all types of health services received by the participant in any health care setting (e.g., physical and mental).

**Costing algorithm.** To assign costs to the utilization data and the mental health professional services used in the BCBT intervention, we will develop a set of unit cost coefficients using the Medical Expenditure Panel Study (MEPS), a nationally representative survey of health care utilization and cost that includes comprehensive assessment of health care services including mental health services (AHRQ, 2004). Similar approaches have been used by other investigators conducting CEA of mental health interventions (e.g., Sherbourne et al., 2001). Health care costs will be converted to constant dollars by using the cost conversion coefficients for a year in the middle of the study period. This approach eliminates the effects of inflation on expenses and removes the burden of adjusting for inflation from the cost and cost-effectiveness models.

**Model fitting.** As described previously, we will collect detailed data to minimize the need to estimate resource consumption. The incremental cost-effectiveness ratio (ICER) will be calculated as the difference in mean cost divided by the difference in the mean PFD. In order to represent uncertainty around the ICER estimate, we will create 1000 bootstrap replications of the data and use these to create 95% confidence interval (Gold et al. 1996). In addition, we will use the bootstrapped data to create a cost-effectiveness acceptability curve (Fenwick & Byford, 2005) to represent the uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would likely consider reasonable. The CEA is constructed by plotting the proportion of the bootstrapped cost and effect pairs that are cost-effective for a range of values of willingness to pay. We have used these methods successfully in previous studies (Lynch et al., 2005), as described in the Preliminary Studies section. The CEA will be conducted by Dr. Lynch in coordination with the HSI and DM committees. Statistical and data management staff at Pittsburgh will be available for data preparation and consultation over the course of the CEA model fitting process.

**Implementation cost estimate.** In our final analysis, we will develop an estimate of BCBT implementation cost. We will carefully document the set-up activities that would be necessary in order to implement the BCBT protocol in a new primary care practice environment (see Measures 5.5.6, ICI). These activities will include time spent training PCCs in case identification and therapists in the BCBT protocol, and we will estimate the cost of periodic retraining (3 year intervals) that would be necessary to maintain model fidelity in practice. In addition, start-up supply costs will be estimated (e.g., printing manuals) designed to reflect a one-year “starter kit” version of the program. As in our CEA, we will exclude research-specific activities such as extensive assessment interviews or maintenance of randomization. Inputs into the implementation cost estimate will be developed with the same costing algorithm as described in the CEA.