Youth Mayo Clinic Anxiety Coach Pilot Study

13-000288 – PILOT

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SPECIFIC AIMS

Consistent with the goals of PAR-12-279 "Pilot Intervention and Services Research Grants (R34)" this R34 proposal seeks to improve the delivery of evidence-based Cognitive Behavioral Therapy (CBT) for childhood anxiety disorders with a recently developed smartphone application, *Mayo Clinic Anxiety Coach*. This application has the potential to 1) increase access to high quality care beyond the brick and mortar mental health setting; and 2) improve the quality and efficiency of face-to-face therapy by promoting and monitoring provider fidelity and patient adherence.

Anxiety disorders are the most common psychiatric disorders in childhood with prevalence rates as high as 15%, but the least likely to be treated (approximately 30%).[1-4] These disorders cause substantial impairment across a variety of domains of functioning, are highly co-morbid with other disorders, and often persist into adulthood.[5-8] Despite efforts to disseminate effective interventions, most patients do not receive empirically supported psychosocial treatment.[9-13] The barriers to meeting the current mental health demand include an insufficient number of practitioners and the limited use of evidence-based treatment, such as exposure therapy, even among self-described anxiety specialists.[14-16] Perhaps as a result of the limited availability of evidence-based treatment, the effectiveness of therapy in clinical settings is significantly lower than the efficacy of therapy in research labs.[17,18] To address the implementation gap, we will need new technologies to not only improve the quality of care being provided in traditional mental health settings, but also to allow patients to receive these interventions through less contact with non-specialist health professionals.[16] A growing body of research suggests that information and communication technology (ICT), such as smartphones, can lead to more out-of-office health-related behavior change than standard paper methods (e.g., diaries or self-help books) through increased convenience, interactivity, and adherence.[19-26] Such interventions may be especially attractive to youth because they contribute to an increased sense of autonomy.[27,28]

The current proposal is part of a larger research program to develop clinically informed methods for increasing access to evidence-based treatment for childhood anxiety disorders. This program recently developed a smartphone application, *Mayo Clinic Anxiety Coach*, based on cognitive-behavioral treatment for anxiety disorders (i.e., exposure-based therapy)[29,30] that can be used as 1) a stand-alone treatment requiring minimal provider contact; and 2) an augmentation of face-to-face treatment that increases clinician fidelity and patient adherence to evidence-based treatment. The design of *Anxiety Coach* is based on evidence and theory[23] suggesting that ICTs are well-suited for encouraging behavior change through 1) scheduled reminders to engage in therapeutic exercises,[31] 2) point of performance support,[32] 3) individually tailored information,[21,33,19] 4) real-time symptom assessment,[34] and 5) readily accessible asynchronous communication.[33] To prepare *Anxiety Coach* for randomized controlled outcome studies, software for patient-provider communication and a protocol for implementation acceptable to patients and providers need to be developed.

To advance *Anxiety Coach* in accordance with guidelines for evaluating ICT to promote health behavior change[35,36] the current project will:

Aim 1: Adapt *Anxiety Coach* for use with a health care provider. During Phase I, a web-based portal that allows providers to monitor symptoms and adherence, provide reminders to complete therapeutic exercises, and communicate asynchronously with patients will be developed and piloted with 15 patients. In addition, community therapists will be identified for recruitment through a survey of current practices conducted under IRB 14-002608 for participation in Phase II.

Aim 2: Assess feasibility, safety, acceptance, and impact on behavior and symptoms of *Anxiety Coach*. During Phase II, 30 therapists will participate in one of three trials to examine the feasibility of using *Anxiety Coach* to increase the frequency of exposure and improve outcomes with varying degrees of face-to-face contact: 1) Reviewing the acceptability of Anxiety Coach and integrating into their practice as desired (n= 30 therapists); 2) Treating children with anxiety disorders with treatment as usual or *Anxiety Coach* with face-to-face therapy, (N = 30 therapists and 30 patients); or 3) Treating children with anxiety disorders with treatment as usual or *Anxiety Coach* with minimal contact (N = 30 patients).

Note: The current modification covers the initiation of Trial 2 and Trial 3. Trial 1 has been approved and enrollment as begun.

Aim 3: Develop a protocol for implementing *Anxiety Coach*. During Phase III, the feasibility data, along with input from patients and therapists taking part in the research, will be analyzed and used to write a

treatment protocol for training therapists to use *Anxiety Coach* for augmenting face-to-face therapy and providing treatment with minimal direct contact.

When completed, this project will deliver a protocol detailing the use of an innovative smartphone technology, *Mayo Clinic Anxiety Coach*, to improve access to effective care for childhood anxiety disorders through 1) providing interventions outside traditional mental health settings with minimal provider contact; and 2) disseminating exposure-based CBT to community practitioners. These results will be used to pursue R01 funding to conduct randomized controlled trials powered to evaluate the symptom improvement and cost-efficiency of using *Mayo Clinic Anxiety Coach* in these settings. By increasing the reach and quality of treatment, *Anxiety Coach* has the potential to improve the outcomes for a large number of children suffering from anxiety disorders.

RESEARCH STRATEGY

Overview. This proposal satisfies the purpose of PAR-12-279 "Pilot Intervention and Services Research Grants (R34)," which seeks to encourage intervention development and service delivery research.

A. SIGNIFICANCE

To increase access to evidence-based Cognitive Behavioral Therapy (CBT) for childhood anxiety disorders, the current proposal will enhance a recently developed smartphone application, Mayo Clinic Anxiety Coach*, and examine its feasibility for providing treatment to patients with limited access to traditional mental health services and for disseminating therapeutic strategies to professionals.*

Anxiety disorders are among the most common psychiatric disorders in childhood with prevalence rates as high as 15%, however they are the least likely to be treated (approximately 30%).[1-4] These disorders cause substantial impairment across a variety of domains of functioning, are highly co-morbid with other psychiatric disorders, and often persist into adulthood.[5-8] Despite efforts to disseminate effective interventions, most patients do not receive empirically supported psychosocial treatment.[4,9-13,15] The barriers to meeting the current mental health demand include an insufficient number of practitioners and the limited use of evidence-based treatment.[14-16] The effectiveness of treatment in clinical settings has been found to be significantly lower than the efficacy of treatment in research labs, likely due to the limited availability of evidence-based treatment.[17,18] However, even with proper training the current brick and mortar mental health establishment does not have an adequate number of providers to address the populations' psychiatric needs.[16] To address the implementation gap, technologies will need to not only improve the quality of care provided in traditional settings, but also allow patients to receive interventions that require less contact with health professionals.[16]

Information and communication technologies (ICT; i.e., web- and smartphone-based applications) have the potential to more efficiently provide health care in a variety of areas including anxiety and depression,[37] eating disorders,[20] and substance use.[38] ICT-based programs provide an appealing option for direct care and treatment dissemination because they are convenient, interactive, and can be individually tailored with little direct contact.[19,21] As such, ICT may be an effective and cost-efficient means to not only disseminate evidence-based practice to clinicians, but to provide high quality care directly to patients. For such programs to be effective they need to provide evidence-based treatment strategies (i.e., CBT) via a medium based on evidence regarding the promotion of health behavior change through ICT.[35,36]

B. INNOVATION

B.1. Dissemination Through Information and Communication Technology (ICT). Mayo Clinic Anxiety Coach *provides the content depth of web-based programs with the point-of-performance tailored messaging possible with a mobile device to affect behavior change outside of the presence of a therapist.*

Health and behavior change programs administered via ICT, similar to *Anxiety Coach,* have a number of features that can improve treatment adherence and outcome including: 1) scheduled reminders to engage in therapeutic exercises,[31] 2) point of performance support,[32] 3) individually tailored information,[19,21,33] 4) real-time symptom assessment,[34] 5) readily accessible asynchronous communication,[33] and 6) attractiveness to

youth through increased sense of autonomy.[27,28] In fact, research has found that ICT interventions provided directly to patients can outperform paper diaries,[21,24] classroom-based prevention programs,[39] standard hospital after care,[20] and shorten the length of traditional CBT.[32] However, shortened interventions have not always been equivalent to standard CBT,[40,41] and most studies have been short-term and without follow-up data.[32] The ability to provide individually tailored feedback in situations where new behaviors are to be performed appears to be an essential feature for increasing adherence and outcome.[21,33] Although research on anxiety disorders has demonstrated the effectiveness of using computer- and web-based treatment programs to increase access to CBT in both children and adults,[32, 42-45] these programs generally have been computer-based and content-rich[42] or mobile devices with limited functionality. More complex mobile device-based programs offering individually tailored treatment content and feedback have begun to show promise for other disorders,[46] but none that have been evaluated scientifically are applicable to child anxiety disorders.

Smartphones present a unique opportunity to reach a large portion of the population including underserved groups. As of September 2012, 59% for those ages 30 to 49, the age range for parents in this proposal, owned a smartphone. In underserved populations, rates are 35% for low income households, 29% for rural areas, and are *higher* for minorities than Caucasians.[47] The majority of the population will likely own smartphones in the near future as 85% currently own a cell phone and the percentage of smartphones versus traditional cell phones is rising, 55% in June 2012 up from 30% in October of 2010.[48] These data suggest that smartphones will be a convenient medium for reaching individuals of all ethnicities, incomes, and regions.

B.2. Evidence-Based Treatment for Childhood Anxiety Disorders. Anxiety Coach *maximizes the likelihood of disseminating CBT to practitioners by providing individually tailored CBT (e.g., fear hierarchies, automated messaging) that accentuates the importance of exposure.*

The treatment content provided by *Anxiety Coach* is based on recent efforts to improve the clinical effectiveness of CBT for child anxiety disorders. Although a wealth of data supports the efficacy of CBT for childhood anxiety disorders,[30,49-51] efforts to transport these interventions into clinical settings have been largely unsuccessful.[18,52-54] One possible factor for the lack of differentiation with usual care may be the infrequent use of *exposure* in effectiveness trials (e.g., 50%-60% of patients compared to upwards of 90% in efficacy trials).[18,30] Exposure is frequently described as the active ingredient in CBT[29,55-62] and, consistent with basic research on the effects of approach and avoidance on children's acquisition of fear beliefs,[63] is hypothesized to allow successful emotional reprocessing of feared stimuli[64] and modification of harm expectancies.[65] The importance of exposure is supported by a review of meta-analyses of adult anxiety treatment finding strong support for exposures, but variable additional benefit from cognitive techniques[66] and outcome studies with children finding improvement only after the initiation of exposure.[67,68] Other possible contributions to the difference between effectiveness and efficacy studies include poorer retention, shorter treatment duration, and lack of protocol flexibility to address comorbidity.[18] Taken together these results suggests that dissemination may be more successful by increasing use of exposure (e.g., community therapists report using *in vivo* exposure approximately a third of time, less often than cognitive and non-evidence-based interventions[14,15]), while preserving flexibility to individually tailor treatment. In fact, recent protocols that encourage exposure early in treatment through the use of decision rules have been more effective than manuals following a more prescriptive session-by-session format.[69,70] In summary, recent research on the dissemination of CBT suggest that protocols specifying a primary active treatment ingredient and allowing the clinician to individually tailor treatment administration may lead to more effective community care than previous approaches.

B.3. *Mayo Clinic Anxiety Coach.* *Currently* Anxiety Coach *delivers individually tailored exposure-based CBT with automated messaging. The proposed study will allow patients to use* Anxiety Coach *with a provider by incorporating asynchronous communication (e.g., text messaging) through a web-based portal and generate data supporting the application's feasibility, safety, and estimated impact.*

Anxiety Coach is an application to deliver CBT for anxiety disorders via iOS (the operating system for the iPhone, iPad, and iPod Touch) that combines the latest research on ICT and CBT dissemination. The content consists of three modules: Assessment, Psychoeducation, and Treatment. The assessment module measures the frequency of anxiety symptoms corresponding to the DSM criteria with a self-report Likert-type scale. The application minimizes patient burden by applying hierarchical decision rules to the patient's responses on a 14-item screener to determine the number of follow-up questions (maximum 21) needed to characterize the

patient's symptoms. The results of the evaluation are presented graphically along with text describing the results and providing tailored recommendations. Patients can track their progress over time by re-taking the assessment and by providing daily ratings of their symptom severity. The second module contains psychoeducational material on the use of *Anxiety Coach*, the cognitive-behavioral conceptualization of anxiety, descriptions of each anxiety disorder, explanations of cognitive behavioral therapy, and guidance for accessing other forms of treatment. The information for each category is easily accessible through 4 to 8 brief segments that typically occupy 1 to 2 screens (less than 400 words).

The central component of the application is the treatment module that guides patients with the help of a parent through the use of exposure therapy. Patients and parents can select from approximately 100 premade fear hierarchies that outline graduated exposure exercises for a wide variety of anxiety symptoms (social situations, panic attacks, separation from loved ones, general worry, obsessions and compulsions, trauma, and specific fears). Patients and parents can also enter text for additional items or use a 4-step wizard to create a unique fear hierarchy. Once a hierarchy is established, *Anxiety Coach* guides the patients and parents through the completion of exposure in real-world situations. This process includes assessing the likelihood and severity of negative outcomes, beginning an exposure (*in vivo*, imaginal, or interoceptive), tracking anxiety graphically during the exposure, receiving prompts to continue until the anxiety has decreased, and evaluating the outcome of the exposure. Patients and parents can record their success by marking exercises as mastered on the fear hierarchy and reviewing their history of completed exposures including the time of completion, the duration of the exposure, and anxiety ratings at the beginning and end. Therapists can review these histories through the mobile device during therapy sessions to assess adherence and provide encouragement.

Anxiety Coach has four features that differentiate it from other applications: 1) coverage of the full range of anxiety disorders; 2) emphasis on exposure, the evidence-based active ingredient of treatment; 3) individualization to the patient's symptoms; and 4) a library of clinical-based exposure hierarchies. A search of the App store, the Internet, library databases, and a list compiled for a survey by the Anxiety and Depression Association of American suggests that no other application has these features. In addition, to our knowledge no smartphone application has a web-based portal for a clinician to track an individual's engagement in, or progress with, treatment. Other applications provide either instruction in relaxation or other non-evidence based interventions, emphasize cognitive restructuring rather than exposure, cannot be individualized, focus on a single disorder, or do not provide a library of pre-existing hierarchies. *Anxiety Coach* is designed to be applicable to individuals across the age range and includes 9 fear hierarchies with social situations specifically for children and adolescents, 8 for childhood separation fears, and 7 hierarchies for childhood phobias. Ongoing pilot testing suggest that children and adolescents have found the current format engaging.

B.4. Evidence-Based Guidelines for Promoting Health Behavior Change with ICT. *By adhering to research and theory on ICT for behavior change, the design of* Anxiety Coach *and the research methodology maximize the potential for creating, and documenting, behavior and symptom change.*

To maximize the efficacy of *Anxiety Coach*, and to ensure the rigor and adequacy of its evaluation, our software design, content, study methodology, and assessments were guided by health behavior research and theory.[23,35] Given that retention can be a challenge for ICT interventions,[71] the user interface design is based on principles associated with retaining users: appealing colors and screen layouts; intuitive, concise navigation and functionality to minimize user burden; and features encouraging interactivity, such as self-tests and self-monitoring.[23,72] Including parents and therapist-support is consistent with the literature associating human contact with better retention.[71] The content of *Anxiety Coach* maximizes the potential for behavior change through evidence-based CBT strategies and ICT functions found to increase effectiveness, such as individually tailored content and point of performance feedback.[21,33] Likewise, we will recruit participants (i.e., therapists with an interest in CBT and children presenting for treatment) that are likely to adhere to the study protocol because they find the content personally relevant.[72] Finally, the research design is intended to answer questions that have been emphasized in guidelines for executing and reporting research on ICT for health behavior change including quantifying the appropriate dose and the degree of professional assistance needed to benefit from *Anxiety Coach*, measuring behavior change (i.e., exposure) hypothesized to lead to symptom improvement, and focusing on safety, data security, and tolerability.[23,35]

B.5. Advancements Made Possible by *Mayo Clinic Anxiety Coach*. To address the unmet need for evidence-based treatment, the current proposal furthers the development of an innovative smartphone technology, *Mayo Clinic Anxiety Coach*, based on advances in disseminating CBT and applying ICT to health behavior change. The content of *Anxiety Coach* is consistent with state-of-the-art flexibly delivered CBT that emphasizes the importance of exposure and individualized feedback through response-based assessment, personalized fear hierarchies, prompts to access the application, encouragement to persist with exposure, and tracking symptoms and performance. The study methodology will address issues of acceptability, adherence, level of support, and safety that are important when evaluating novel ICT interventions. When completed, the data from this project will provide a protocol detailing the use of *Mayo Clinic Anxiety Coach* to 1) promote and monitor provider fidelity to evidence-based practices, and 2) allow patients to access effective care outside traditional brick and mortar mental health settings. By increasing the reach and quality of treatment, *Anxiety Coach* has the potential to improve outcomes for a large number of children suffering from anxiety disorders.

C. APPROACH

C.1. Overview. In this proposal we will augment *Anxiety Coach* with functions that facilitate patient-provider communications and feedback. We will then do a small-scale deployment of the enhanced software as a tool to a) facilitate use of evidence-based practices within face-to-face therapeutic encounters, and b) provide CBT to patients with infrequent face-to-face contact, carefully examining its acceptability, ease of use, and need for contact. Findings from this deployment will be used to develop a protocol for implementing and testing within a future randomized controlled trial. During **Phase I** we will a) develop a web-based portal for practitioners to monitor symptoms and adherence, provide reminders to complete therapeutic exercises, and communicate asynchronously with patients; b) pilot *Anxiety Coach* with 15 patients; and c) recruit therapists for participation in Phase II through a survey conducted under IRB 14-002608 of community practice. During **Phase II** the feasibility, safety, acceptance, and influence on behavior will be assessed by having up to 70 therapists participate in one three trials to examine the feasibility of using *Anxiety Coach* to increase the frequency of exposure and improve outcomes with varying degrees of face-to-face contact: 1) Reviewing the acceptability of Anxiety Coach and integrating into their practice as desired (n= 30 therapists); 2) Treating children with anxiety disorders (with the support from study personnel) using treatment as usual (TAU) or *Anxiety Coach* with face-to-face therapy (FTF-AC); or 3) Treating children with anxiety disorders (with the support from study personnel) using TAU or *Anxiety Coach* with minimal contact (MC-AC). During **Phase III** the feasibility data will be analyzed and used to write a protocol for training therapists to use *Anxiety Coach* to augment face-to-face therapy and provide treatment with minimal contact.

Note: The current modification covers the initiation of Trial 2 and Trial 3. Trial 1 has been approved and enrollment as begun.

C.2. Preliminary Studies for the Development of *Mayo Clinic Anxiety Coach*

C.2.a.Test Version. The development of *Anxiety Coach* began with a test application created by Drs. Whiteside and Duncan that allowed patients and their parents to provide daily ratings of symptom severity and record anxiety during exposure exercises. Therapists then monitored through a secure webpage the patient's symptoms, the fear hierarchy items targeted for exposure, the patient's anxiety ratings during the exposure, and number of exposures completed. This information allowed the therapist to assess the family's adherence to treatment recommendations as well as symptom response without a face-to-face meeting. The test version was piloted with 4 child-parent dyads seeking treatment for generalized anxiety disorder, specific phobia, and obsessive compulsive disorder (x2) through the Mayo Clinic Pediatric Anxiety Disorder Clinic. All families rated the application as "very helpful" and "very easy to use" (the top rating on a four-point scale). The families accessed the program on 56% of days, suggesting that intervention was moderately integrated into the families routine compared to once or twice weekly homework[73] with treatment manuals and an ICT intervention for eating disorders.[20,21] Each family indicated that they would like to be able to use the application to communicate with the therapist, suggesting that increased functionality would increase the frequency of use.

C.2.b. Intervention Development. While the test version supported the feasibility of engaging families in assignments outside the therapy session, the application lacked therapeutic content and communication functionality. To develop the content for *Anxiety Coach* we reviewed the literature supporting the efficacy of the CBT for childhood anxiety disorders.[30,51,69] However, the studies providing the majority of this support utilized manualized approaches with limited flexibility[30,74] that have underperformed in community settings.[18,54] Thus, we modeled the treatment content on more flexible, individually tailored protocols emphasizing exposure that have resulted in more successful dissemination.[69,70] We then examined the feasibility, acceptability, and impact of this treatment as delivered through a non-ICT format.[75-77] In a retrospective study[75] and a prospective study[77] characterizing the delivery of treatment components with anxious youth in our clinic (Ns of 43 and 28 respectively), treatment was generally shorter (8 to 9 vs. 14 to 16 sessions) and included exposures earlier (3rd or 4th vs. 10th session) than in traditional manualized interventions in efficacy and effectiveness studies. Exposure begun earlier resulted in more patients receiving exposure than in effectiveness studies (100% vs. 59%) and greater use of exposure was associated with more improvement in functioning (r = .32). Both studies found large pre to post effect sizes among treatment completers for parent-reported symptoms (1.47 and 1.82) and functioning (1.72 and 1.24). A third study suggests that the exposure-focused approach prepares families to maintain improvement after the termination of direct therapist contact. In this uncontrolled examination, 15 youth completed a 5-day intensive treatment for OCD. Baseline scores on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) in the severe range (m = 28.3, *s.d.* = 5.0) decreased to a moderate level (m = 16.3, *s.d.* = 6.4) immediately following the intensive week and continued to decline to the mild range (m = 11.8, *s.d.* = 7.5) over the next four months without direct therapist contact.

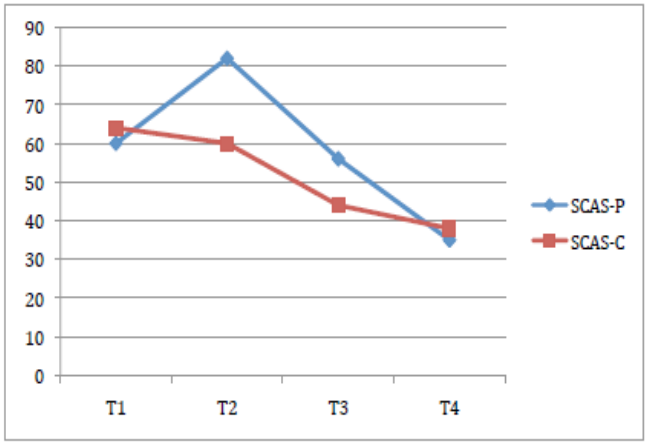

Figure 1

C.2.c. Application Development. Following the development of the test version and treatment content Drs. Whiteside, Abramowitz, and Duncan received a CoDE Fund (Connect, Design, Enable) Grant from the Mayo Clinic Center for Innovation in 2010 to develop the current version of *Mayo Clinic Anxiety Coach* described above (Section B.3). The goal was to design an application that had comprehensive content to be a stand-alone intervention; flexibility and responsiveness to be individually tailored; an intuitive interface to be used independently; a simple and interactive design to retain users; and functionality to interact with a therapist. Over a 6-month period Drs. Whiteside and Abramowitz created the therapeutic content based on the literature and their expertise in CBT for anxiety, Dr. Duncan developed the supporting software, and the Center for Innovation conducted a workshop with mental health providers, medical professionals, and designers to maximize the utility of the final product. The resulting beta version was submitted to a focus group of individuals from varied backgrounds with limited knowledge of mental health treatment. Through an iterative process of collecting feedback from the initial focus group and additional therapists, experts in systems and procedures, and laypersons the team simplified and refined the content and design.

Anxiety Coach was then piloted with two patients: a 14-year-old girl presenting for a week-long intensive treatment for panic disorder with agoraphobia, separation anxiety disorder, GAD, and OCD; and a 12-year-old girl, using *Anxiety Coach* as an adjunct to stalled progress in individual CBT for OCD. Both patients used the application to complete exposures approximately twice per week, and described it as helpful and engaging. The first patient's symptoms as measured by self- and mother-report on the Spence Children's Anxiety Scale, remained stable during baseline prior to treatment, improved during the 1-week treatment and continued to improve during the follow-up period with no direct therapist contact (Figure 1). The second patient experienced minimal symptom improvement over 2-months (CY-BOCS 21 to 18). This piloting supported the feasibility of the application, but reiterated the importance a mechanism for therapists to monitor and communicate with the patient. Pilot testing continues with an additional 6 anxious patients and *over* 2000 users have downloaded

Anxiety Coach from the App Store. The data from our lab and online reviews will be used to guide refinement of the application prior to and during Phase I of the Study.

C.2.d. Summary and Justification for Funding. To build on the initial development and pilot testing, funding is necessary to create the web-based portal; and evaluate the feasibility, acceptability, safety, and impact of *Anxiety Coach* to disseminate evidence-based CBT and provide a minimal contact intervention. Funding is needed to create and refine the clinical content and feedback components of the web-portal as well as to develop the software that supports the portal. Funding is also needed to support the recruitment of community therapists and patients, conduct assessment and treatment, analyze data from the feasibility study, prepare scientific reports, and to develop the procedures and protocols for testing *Anxiety Coach* within an RCT.

Each of the investigators and consultants has considerable experience that support the successful completion of the proposed project: (1) Dr. Whiteside has extensive experience in exposure-based CBT for childhood anxiety disorders, as well as the development and evaluation of treatments; (2) Dr. Vickers Douglas has expertise in qualitative and quantitative assessment, (3) Dr. Abramowitz is an internationally known anxiety disorder researcher with expertise in treatment evaluation; (4) Dr. Duncan has created multiple healthcare-related applications for the iOS platform; (5) Dr. Ollendick is an internationally recognized expert and leading figure in the development and evaluation of treatments for childhood anxiety disorders; (6) Dr. Andersson is a leading authority on the development of ICT-based psychological interventions; and (7) the Principal Investigator's (PI's) site is an internationally recognized medical center with extensive resources including biostatistician services, a center for the development of medical information technology, and an extensive network of community mental health providers contracted through an affiliated insurance plan.

C.3. Study Design

C.3.a. Study Phase I: Web Portal Design, Use & Procedures Manual Development, Open Pilot, and Therapist Recruitment: (14 months). Study Phase 1 addresses Aim 1 of preparing *Anxiety Coach* for use with health care professionals through four interlocking activities.

C.3.a.1. Development of a Web-Based Portal. During the first four months Drs. Whiteside and Abramowitz will develop the content of a web-based portal that enables a health care provider to asynchronously monitor and communicate with patients using *Anxiety Coach*. Information from the patient's device (e.g., symptom ratings, target and duration of completed exposures) will be automatically uploaded to the web-based portal, which the provider accesses from a computer. The portal will be a webpage through which the therapist can quickly review a) whether the patient is using the application, b) the patient's current symptom level, and c) communicate with the patient electronically. The homepage will display all of the therapist's patients actively using Anxiety Coach. Each name will be followed by the patient's recent use of *Anxiety Coach* including the number of exposures completed over the past week, change in symptom ratings, and the presence of any messages or activities (i.e., reassessment) that need attention. From the home page the therapist can select a patient from the list to access more detailed information including: a) frequency and duration of time spent by the patient on the application; b) logs of completed exposures including item, anxiety ratings, duration, and outcome; c) graphics of daily symptom ratings; d) the fear-hierarchy with mastered items; e) summaries of assessments; and d) a log of communication with the patient. The provider will be able to compose and send messages to the patient; enable automated reminders and messages; generate progress notes; or schedule interactions (e.g., phone call, videophone, in person meeting). In addition, the web-based portal will track the amount of time therapists spend on a patient's case outside of therapy sessions. The *patient's* interface through the *Anxiety Coach* application will be enhanced with embedded instructional videos, increased child friendly features (e.g., interactive educational materials, graphics for the To Do List), capability to message and schedule with the provider, and automated reminders. The software to implement these features in a secure fashion will be completed by Dr. Duncan over the first eight months. The system will employ industry-standard security practices to ensure the protection of sensitive data and adhere closely to applicable health technology standards including HIPAA and preliminary guidance from the FDA on mobile medical software.

C.3.a.2. Development of a Use and Procedures Manual (UPM). During the first 8 months Dr. Whiteside with consultation from Dr. Abramowitz will develop a Use and Procedures Manual (UPM) to guide the therapists and the study personnel that support them. The therapist section will consist of: a) a treatment rationale and background; b) a curriculum for using the *Anxiety Coach* to introduce patients to the application and exposure-based CBT; c) minimum standards for the frequency that therapists monitor patient use of *Anxiety Coach*, d) thresholds for determining when patients are not adhering to treatment or progressing adequately; e) instructions for intervention when patients fail to meet thresholds; f) procedures for assessing and responding to crises, comorbidity, and safety issues; and g) decisions trees for initiating additional face-to-face contact. The section for the study personnel that support the therapists will include: a) a curriculum for training therapists on *Anxiety Coach*, exposure-based CBT, and the therapist guidelines; b) minimum standards for the frequency that support personnel monitor therapist and patient access of *Anxiety Coach*; and c) instructions for how to intervene when therapists are not meeting minimum standards for monitoring their patients. The above guidelines for therapists and support personnel will be presented with appropriate modifications for FTF-AC versus MC-AC. In addition, a comparable set of instructions to orient therapists to the study procedures and guidelines for TAU will be created. The protocol will be reviewed by the entire study team including consultants Dr. Thomas Ollendick as an expert in child anxiety disorders treatment research and Dr. Gerhard Andersson as an expert on the ICT delivery of psychological treatments.

C.3.a.3. Open Pilot Trial. During months 8 through 14 the web-based portal, the procedures in the UPM, and the assessment methodology for Phase II will be piloted in an open trial of up to 15 patients using *Anxiety Coach*. Two therapists within the Pediatric Anxiety Disorder Clinic and with extensive experience providing exposure-based CBT to children with anxiety disorders and the use of *Anxiety Coach* will administer the intervention. In addition, two therapists in primary care with experience treating anxious children will each see 1 to 2 patients. Half of the patients seen by each therapist will follow the FTF-AC protocol while the other half will be treated with MC-AC protocol. Dr. Whiteside will provide support to therapists. Staff from Mayo Clinic HealthCare Policy & Research under the supervision of Drs. Vickers Douglas will conduct qualitative interviews with patients, parents, and clinicians to elicit information regarding the design, content, usability, and satisfaction with FTC-AC, MC-AC, and the UPM. Drs. Whiteside, and Duncan with consultation from Dr. Abramowitz will review data regarding symptom change, exposure use, and use of *Anxiety Coach* to examine whether patients made acceptable improvement (defined as equal or greater to outcomes found previously in our clinic and in published trials) and qualitative data regarding patient and therapist experience to revise *Anxiety Coach* and the intervention protocols.

C.3.a.4. Recruitment of Community Therapists. Simultaneously to the steps outlined in C.3.a.1 to C.3.a.3, a survey will be conducted under IRB 14-002608 to identify and recruit therapists for participation in Phase II. The survey will be administered through the Mayo Clinic Survey Research Center and will be sent to outpatient mental health therapists. This panel includes 1111 mental health providers (25% clinical social workers, 17% psychiatrists, 16% master's professional counselors, 13% Ph.D. psychologists, 10% marriage and family therapists, 7% PsyD psychologists, and 5% nurse practitioners) practicing in a variety of settings (54% regional clinics, 22% private or group practice, and 14% in a major medical center). The practitioners are in 45 counties across southeastern Minnesota, northern Iowa, and western Wisconsin with 45% in counties, excluding major metropolitan areas, designated by the U.S. Department of Health and Human Services as Mental Health Care Health Professional Shortage Areas.[78] The survey will inquire about theoretical orientation, number of children with anxiety disorders seen, use of a variety of therapeutic strategies including exposure, and beliefs about exposure. The survey will be sent electronically. Non-responders will be sent a second email. This procedure typically results in a 30 to 40% response rate. Therapists in underserved counties (excluding the major urban centers) that report treating children with anxiety disorders, openness to CBT, and infrequent use of exposure will be recruited for participation in Phase II. In addition, data will be used to characterize the frequency with which evidence-based therapy is provided within the community.

In response to concerns expressed by the funding agency regarding recruitment, the recruitment plan was amended to include contacting therapist in region through Minnesota State licensing boards mailing list and professional organization communications. This plan was approved under a separate IRB proposal (IRB # 14-

002608). This process has been completed and resulted in approximately 20 therapists that have completed the enrollment process. In effort to increase enrollment of therapist we will take the following actions: 1) Re-send an email invitation to all therapists with email addresses on file with the most current state licensing boards (e.g., psychology and social work), 2) Re-send an email invitation to all therapists with the Mayo Health System, 3) Contact agencies and organizations in Minnesota providing childhood mental health services via email and phone to invite therapists to participate. Based on previous lists we anticipate that we will send invitations to approximately 8,000 therapists.

In response to the IRB's decision that therapists in Trials 2 and 3 will be engaged in research activity, participation in Trials 2 and 3 will be limited to therapists within Mayo Clinic (Rochester and Health System) and external organizations that have an IRB and with which we complete a reliance agreement. Recruitment of therapists within Mayo Clinic (Mayo Clinic will be used to refer to Rochester and Health System) will be conducted by the study staff (PI, study coordinator, intervention specialists) directly through emails and phone calls (scripts included in this modification). In addition, study staff will provide the recruitment scripts to division leaders and supervisors to ensure that recruitment and participation in the study is consistent with clinical programming. Finally, the study staff will provide recruitment materials to members of the Convergence Child Specialty Council to provide interested clinicians with familiar contact to discuss the study. All efforts to recruit clinicians will emphasize the voluntary nature of the study and that declining to participate will have no effect on their employment or care through Mayo Clinic. Our study staff will directly contact external institutions that provide child mental health care to determine if they would be interested in partnering in this project. Only institutions that have at least 5 interested and appropriate therapists will be contracted with. We anticipate entering agreements with up to 4 organizations in order to enroll 30 therapists for Trial II. The Mayo Clinic IRB will serve as the IRB of record for the collaborating institutions. Recruitment of therapists within the partnering institutions will be implemented by a site-PI following the procedures consistent with those used within Mayo Clinic. Trial 3 will involve therapists from the study staff providing treatment.

Therapists that are interested in participating but are not covered by an IRB, will be enrolled in the first trial, i.e., acceptability study.

C.3.b. Phase II: Therapist Trials (18 months). The second phase of this proposal will address Aim 2 of assessing the feasibility, safety, acceptance, and impact of *Anxiety Coach* through three trials.

Note: The current modification covers the initiation of Trial 2 and Trial 3. Trial 1 has been approved and enrollment as begun.

Trial 1. In Trial 1 (Acceptability) we will gather acceptability and usability data from up to 30 therapists. After being consented therapists will complete a packet of information about how they treat child anxiety and their beliefs about treatment related issues. Each therapist will then receive training from a study intervention specialist on how to use Mayo Clinic Anxiety Coach. The therapists will be given access to use Mayo Clinic Anxiety Coach and be given an iPod Touch and can incorporate it into their practice as they desire for a period of six months during which time the therapists will have access to the intervention specialist to answer questions about how to use the application. To protect patient confidentiality, the system will generate numerical identifiers (e.g. Patient #1) and therapists will only be able to enter ages into the system, rather than full names and birthdates. Therapist will be asked to complete questionnaires about how they treat child anxiety and their beliefs about treatment related issues as well as questionnaires about usability and how they integrated Anxiety Coach into their practice two weeks and six months after completing the training. In addition, data automatically recorded through any use of the application will be analyzed.

Trial 2. In Trial 2 (Increasing Exposure Use) 30 therapists will be randomized to treat 30 children with anxiety disorders with treatment as usual or FTF-AC. (If necessary due to limited therapist availability, therapists randomized to TAU will treat a second patient with FTF-AC).Therapists and patients/parents will be consented. Data collection will include questionnaires completed by therapists, patients, and parents before and after treatment, as well as audio recordings of sessions, and data automatically saved by the application.

Trial 3. In Trial 3 (Increasing Access) children with anxiety disorders will be randomize to receive with MC-AC delivered by therapists in the Pediatric Anxiety Disorders Clinic (study staff) or treatment as usual in the community or within Mayo Clinic, just not with their current therapist. Data collection will include questionnaires completed by therapists, patients, and parents before and after treatment, as well as data automatically saved by the application. Following the study all patients will be offered treatment within the Pediatric Anxiety Disorders Clinic. Patients in the community treatment group will also receive the Anxiety Coach application.

C.3.c. Phase III: Revision Stage (4 months). During the final 4 months the feasibility data will be analyzed along with feedback from patients and therapists. This data will be used to revise the protocol for training therapists to use *Anxiety Coach*, prepare a manuscript for publication, and apply for R01 funding to conduct a fully powered randomized controlled trial to evaluate the symptom improvement and cost-efficiency of using *Anxiety Coach* to provide minimal contact care and disseminate evidence-based treatment.

C.4. Participant Availability and Recruitment. The outpatient mental health therapists in Trial 2 will be recruited and will subsequently recruit their own patients into the study. The therapists will be provided an iPod Touch for participating in the study that they can keep. Before recruiting patients, therapists will complete appropriate training in research ethics. Patients will be recruited by the therapists during their initial evaluation. Patients will be screened and consented by study staff. Patients **and therapists** in each condition will be reimbursed for completing study assessments and recordings ($100 total) and will receive an iPod Touch that they can keep. Partnering institutions in the minimal contact condition can be reimbursed for non-billable time spent on the *Anxiety Coach* portal at a rate of $146.34 per hour up to 6 hours. The therapists for Trial 1 have largely been recruited under the initially approved IRB protocol. Additional therapists will be recruited as needed.

C.4.a. Inclusion Criteria. *Therapists*: 1) Treat child anxiety patients; 2) Current license as a mental health professional (e.g., psychologist, clinical social worker, marriage and family therapist, professional counselor); and 3) competence to provide therapy to youth based on review of institutional or state licensing records. *Patients*: 1) Youth between the ages of 7 and 17 presenting for outpatient therapy with a principal diagnosis of social phobia, separation anxiety disorder, panic disorder with and without agoraphobia, specific phobia, or obsessive compulsive disorder (based on structured interview, additional available information and consensus of Dr. Whiteside and evaluator); 2) A parent or other primary care giver available to participate with the child in all assessment and treatment activities; and 3) English speaking.

C.4.b. Exclusion Criteria. *Therapists*: 1) History of investigation or disciplinary action (based on review of institutional records), Trials 2 and 3 only; and 2) Opposition to CBT per survey responses. *Patients*: 1) History of and/or current diagnoses of: psychosis, autism, bipolar disorder, mental retardation, oppositional defiant disorder, selective mutism, PTSD, or major depressive disorder measured by structured interview and all available clinical information; 2) current suicidality as assessed by the depression module of the structured diagnostic interview and the CDI-S; 3) A positive diagnosis in the caregiver of mental retardation, psychosis, or other psychiatric disorders or conditions limiting their ability to understand CBT (based on clinical interview); 4) an adequate trial of CBT for the child of any psychiatric disorder based on clinical interview; and 5) Initiation or dose change of an antidepressant for the child within 8 weeks or an antipsychotic within 6 weeks of enrollment. Patients and their prescribers will be encouraged to refrain from changing psychotropic medications or dosages during the study without consulting the study staff (Human Subjects); changes will be recorded and analyzed.

C.5. Interventions. Each therapist will be randomized to treat one or two patients with TAU or FTF-AC. The general intervention structure is consistent across treatments to avoid confounding variations.

C.5.a. General Intervention Structure. In Trial 2, prior to each patient beginning treatment an intervention specialist will conduct a 30 to 90-minute training session with the therapist via phone and provide an electronic version of the protocol. Before the training with the intervention specialists, therapists providing treatment with AC therapists will have an additional phone call with the study coordinator to receive assistance accessing the

technology, In each condition the therapist will provide 6 to 12 treatment contacts over the 12-week period. These parameters are based on the median and modal number of sessions attended by patients in the our clinic (6)[77] and the number of sessions in the seminal trial of childhood anxiety treatment (12).[30] The frequency of these session is expected to be weekly for approximately the first month and then can be based on therapist's clinical judgment. These requirements are to ensure that patients receive a sufficient treatment dose to compare therapist behavior across conditions. In each condition of Trial 2 an intervention specialist will: 1) Review each patient weekly; 2) respond to therapist inquires within 24 hours; and 3) contact therapists not adhering to the protocol. In Trial 1 the therapists will be able to contact an intervention specialist over with question about how to use Anxiety Coach for a six-month period following the initial training.

C.5.b. Treatment as Usual (TAU). In the TAU condition (Trial 2) therapists provide treatment consistent with their orientation and clinical judgment. Previous research suggest that TAU will include supportive therapy, relaxation, and cognitive restructuring.[15] The format of treatment will be 6 to 12 50-minute face-to-face therapy sessions in the therapist's office, with flexibility to leave the office (e.g., for exposure). Therapists can communicate with patients between sessions (e.g., phone calls), as long as this medium is not the primary mode of treatment. In preparation for TAU the project director will train therapists in: 1) teaching patients and caregivers to record daily symptoms with the iPod Touch; 2) audio recording sessions; 3) the role of the project director to track progress and provide support; and 4) the guidelines regarding the structure of sessions.

C.5.c. Face-to-face Treatment Using *Anxiety Coach* (FTF-AC). In this condition therapists will provide 6 to 12 50-minute face-to-face therapy sessions using *Anxiety Coach*. As with TAU, the sessions are expected to initially occur weekly and be within the office although the therapist can leave the office to conduct exposure. The therapist is encouraged to utilize *Anxiety Coach* within the session, encourage the patient to use the application to complete homework, and review progress in-session via the web-based portal. In preparation for this condition the project director will train each therapist in using *Anxiety Coach* within therapy including: 1) a brief overview of the cognitive behavioral model and demonstration of the psychoeducation component of the application; 2) demonstration of the assessment aspects of the application and instructions on how to direct patients to take the self-test and provide daily ratings; 3) introduction on how to construct a fear hierarchy using *Anxiety Coach*; 4) demonstration of how to conduct exposure exercises with cognitive restructuring using *Anxiety Coach*; 5) introduction to use of the web-based portal to monitor patient use of the application, 6) discussion of the procedures for the project director to monitor use of the application and how to contact them for assistance; and 7) the guidelines regarding the structure of sessions.

C.5.d. Minimal Contact Treatment Using *Anxiety Coach* (MC-AC).
In this condition, the therapist will meet with the patient and parent for a 50-minute face-to-face session to provide a tutorial on the use of *Anxiety Coach*. Therapists will be allowed 2 additional face-to-face sessions if necessary and still remain in protocol. The therapist is expected to review the patient's progress via the web-based portal and communicate with the patient electronically at least once per week for a total of at least 6 and up to 12 weeks of intervention. In preparation for this condition the project director will train therapists (all study staff) on using *Anxiety Coach* as in the FTF-AC training (**C.5.c**) with the exception of 7) the guidelines regarding the structure of *contacts* (rather than sessions).

C.5.e. Treatment as usual (TAU). The control condition in Trial 3 will consist of having the family participate in the existing clinical services offered by the therapist over the 12-week period. After 12-weeks they will be asked to sign a release of information to have the any outside treatment records sent for review by the study staff. The records will be coded for treatment components. As the post-study evaluations, patients in the TAU condition will receive Anxiety Coach and be offered additional treatment as needed.

C.6. Design Considerations

C.6.a. Justification of Experimental Design. The use of three conditions across two trials allows for an examination of the effects of *Anxiety Coach* and direct therapist contact. Specifically, the **TAU vs. FTF-AC comparison** provides an estimate of the feasibility and palatability of *Anxiety Coach* to therapists, a measure

of the extent to which the application facilitates therapists' use of exposure-based methods, the usefulness of *Anxiety Coach* for disseminating evidence-based CBT methods to community therapists, and its value for facilitating treatment adherence among patients with anxiety disorders. Randomizing therapists/patients to one of two conditions removes the potential for bias to affect recruitment, keeps the evaluators blind to experimental condition, removes concerns with order effects, and allows for the more patients to be treated simultaneously thus decreasing the length of the study. **The MC-AC vs. TAU comparison** provides an estimate of the feasibility as well as the impact on acceptability and outcome of using *Anxiety Coach* with limited direct therapist contact as a method for extending treatment outside of the brick and mortar mental health settings. To increase the real-world generalizability of the study, the study will not pay for therapy, but patients in all conditions will be reimbursed for participation in assessments and will be allowed to keep the iPod Touch.

C.6.b. Inclusion of Treatment as Usual. The inclusion of TAU provides a more stringent and naturalistic test of the relative feasibility and benefits of *Anxiety Coach* than use of no-treatment or non-specific active placebo. In addition, a TAU control group does not require training of therapists. On the other hand, although exposure is rarely used in community practice,[15] it is possible that TAU may include exposure and thereby dilute the effect of the TAU vs. FTF-AC comparison. To decrease this possibility, recruitment will focus on therapists who report infrequent use of exposure. In addition, the content of TAU sessions will be recorded and coded to document the use of exposure. Other alternatives, such as a waitlist control group, non-specific active placebo, or medication would not test the impact of *Anxiety Coach* on therapist use of exposure. Practical obstacles would make it extremely difficult to provide pharmacological care in a safe manner, as the targeted population includes families living some distance from the study site.

C.6.c. Impact of Translating CBT into an ICT Platform. Because the current design does not compare *Anxiety Coach* to traditional CBT it cannot examine the costs or benefits of translating CBT to an ICT platform. Although *Anxiety Coach* has the potential to enhance patient adherence and the efficiency of CBT, given the limited availability of CBT providers, increasing reach through dissemination and minimal contact treatment addresses a more pressing need. As such, a comparison between minimal contact *Anxiety Coach* and face-to-face CBT would have less impact of increasing the reach of evidenced-based care than the proposed design.

C.6.d. Impact of *Anxiety Coach* vs. Other Treatment Aides. The current design controls for the effect of introducing ICT into therapy by including an iPod Touch to track symptoms in the TAU condition. However, the study does not compare *Anxiety Coach* to other electronic or paper treatment-aides. Such questions about the relative value of *Anxiety Coach* compared to other interventions delivered would be more appropriately addressed after the feasibility and beneficial effects of *Anxiety Coach* have been established.

C.7. Procedures

C.7.a. Therapist Survey. A survey will be sent to all the mental health providers contracted by MMSI under IRB 14-002608. Therapists that practice in areas designated by the U.S. Department of Health and Human Services as Mental Health Care Health Professional Shortage Areas,[78] treat children with anxiety disorders, endorse openness to CBT, and report infrequent use of exposure will be recruited into the study.

C.7.b. Therapist Telephone Screening and Consent. Therapist eligibility and interest in participating in the study will be assessed through phone screening completed by the study team. Information regarding licensure status, frequency of treating children with anxiety disorders, and openness to piloting a smartphone-based CBT aide will be confirmed by the therapists' institution. Therapists that meet inclusion/exclusion criteria will be mailed a consent form.

C.7.c. Patient Telephone Screening. For Trials 2 and 3, a multi-gate screening procedure will be used to recruit patients. Interested patients evaluated as part of clinical practice by participating therapists will be an informational letter, instructions, two copies of the consent/assent documents, parent- and child-report forms, and instructions to contact the study team for pre-consent screening. Therapists will also relay patient name and information to study staff via telephone for contact. During the screening call, information regarding the

patient's symptoms, previous treatment and diagnoses, and willingness to be assigned to one of three treatment conditions will be gathered. The number of callers deemed ineligible and reasons for ineligibility will be recorded in the Screening Log. If patient is likely to be eligible, a consent and evaluation videophone visit will be scheduled. This visit should occur within 1 week (+/- 1 week) from the initial therapist visit.

C.7.d. Consent and Evaluation. For Trials 2 and 3 the videophone consent and evaluation visit should be completed within 1 week (+/- 1 week) from the initial therapist visit and will be organized into two parts: 1) Consent and 2) Evaluation. During the Consent phase, the consent/assent documents will be reviewed and all parties will be given adequate opportunity to ask questions. Specific areas of the consent/assent will be re-reviewed if deficits in understanding are identified. If consent/assent is signed, completion of the Evaluation phase of the visit will commence. If signed consent/assent is not received, the patient will not be enrolled and the information will not be used. Patient eligibility will be formally determined during the Evaluation phase by an independent evaluator blind to the therapy condition under the supervision of Dr. Vickers Douglas. At this time the child and parent will complete paper and pencil measures as well as interviewer administered structured diagnostic interviews. The feasibility of conducting assessments via videophone has been demonstrated in a recently completed multi-site study of an intensive treatment with 20 children diagnosed with OCD coordinated by Dr. Whiteside. In this study 100% of the OCD diagnoses made at the initial evaluation via videophone were confirmed with face-to-face assessments completed after a one-month no-treatment period. Preliminary data suggest that 67% did not meet criteria for OCD after the evaluation and scores on interview administered continuous measures decreased by 65% suggesting that videophone assessments are sensitive to treatment. Access to ICT did not appear to harm recruitment as 100% of the families who expressed interest in participation already had access to the Internet prior to study enrollment. At the end of the videophone evaluation, caregivers will be instructed to return signed copies of consent/assent forms and completed parent- and child-report forms in the postage-paid envelope to study staff as soon as possible. Patients will not be considered enrolled in the study until the signed consent/assent documents have been received and signed by study staff. Patients for whom consent/assent is not returned will be considered screen failures, and data collected prior to receiving consent will not be included in any research-related activities.

If therapists in Trial 1 choose to use Anxiety Coach in their practice during, those patients will not be engaged in any research activities. In order to use the application the patient must agree to the terms of use that explain what data Mayo Clinic collects and how these data are used.

C.7.e. Treatment Assignment. For Trial 2, therapists will be randomized to either TAU or FTF-AC after they are consented. The therapist will then offer participation to the next patient they see likely to qualify. (If needed, the second patient treated by a therapist randomized to TAU will be enrolled in the FTF-AC condition.) This format clearly differentiates the therapists' participation in the study from the patients' participation. To limit bias in enrollment, neither patients nor the independent evaluators will be aware of therapeutic condition at the time of enrollment. Treatment in each condition can begin within 1 to 2 weeks of the evaluation as soon as the patient has completed the study evaluation. All patients will be informed that participation in the study includes the possibility of enrollment into either of two conditions. If patients discontinue treatment prematurely, before the sixth session, they will not be replaced with another patient. Instead efforts will be made to complete early withdrawal post-treatment evaluations on all enrollees and the frequency of premature discontinuation will be compared between conditions. For Trial 1, the therapists will have access to the Anxiety Coach application and can use it as they choose in their clinical practice. For Trial 3, treatment assignment will occur following consent and the pre-evaluation is completed.

C.7.f. Therapists, Treatment Integrity and Competence. Therapists in Trials 2 and 3 will provide treatment. To determine the success of creating conditions with distinct therapist behavior, all sessions and communication in each condition will be recorded and coded for use of exposure and other interventions. In the TAU condition, the therapist will not receive any instruction regarding the content of treatment. In all three conditions across the two trials the intervention specialists or the PI will monitor and support the therapists' compliance with guidelines. The intervention specialists have highly developed therapeutic skills, at least five years' experience providing CBT to children with anxiety disorders and their families, extensive one-on-one

supervision from Dr. Whiteside, attendance of workshops on anxiety treatment, and been involved in the development of *Anxiety Coach*. Dr. Whiteside will train the intervention specialists in the procedures outlined in the UPM for supporting therapists, meet weekly for supervision, and provide additional supervision as needed for concerns about a therapist's use of the study interventions or a patient's progress, clinical deterioration, or development of new symptoms.

C.7.g. Assessment Timeline. Patient participants will receive two assessments conducted via videophone by a trained independent evaluator blind to condition under the supervision of Dr. Vickers Douglas. The initial assessment will be conducted at baseline (Time 1) when the patient's eligibility is determined. The patient will begin treatment within one to two weeks. The patient's response to treatment will be assessed 12 weeks (+/- 2 weeks) after the initial treatment session (Time 2). The evaluations will be comprehensive in nature (e.g., diagnostic interview, clinician ratings, parent- and self-reports). Accommodations will be made for families without electronic access, such as videophone assessments in the therapist's office. Beginning at the baseline assessment and continuing throughout the study, patients will rate their daily symptoms with an iPod Touch. Therapists in Trial 1 will complete the survey materials from Phase I inquiring about treatment practices and beliefs prior to receiving training in the use of Anxiety Coach. Two weeks after receiving Anxiety Coach training the therapists will be asked to complete the same survey material plus measures assessing software usability. 6 months after the initial training, therapist will be asked to complete the survey material, usability measure, and a questionnaire about their actual use of Anxiety Coach since the training.

C.7.h. Additional Treatment. During Trials 2 and 3 participants will be asked to refrain from participating in additional treatment during the study (i.e. other therapy, initiating or changing medications). Following the post-treatment evaluation patients can continue with their therapist or seek other treatment. Patients in the TAU condition will be provided *Anxiety Coach* and treatment recommendations after the post-treatment evaluation. Given that many children are treated with medication before being referred for therapy, restricting participation to medication-free patients would interfere with enrollment. Medication changes during the study will be recorded and analyzed.

C.8. Procedural Considerations.

C.8.a. Age Range. A relatively broad age range will be included to evaluate the feasibility of utilizing *Anxiety Coach* with children at different developmental levels. Although the proposed agent of change (cognitive change through exposure) is theoretically consistent across the age range, therapists will be allowed freedom to administer these techniques in a developmentally sensitive manner, e.g. allowing more independence with adolescents, less discussion of cognitions with children. The current proposal focuses on youth as this population is at particularly high risk of not receiving effective treatment, has an high level of familiarity with ICT, and has been found to be particularly motivated by the introduction of ICTs into treatment.[4,27,28]

C.8.b. Inclusion of Patients with Comorbid Disorders. Children with multiple anxiety disorders or additional diagnosis (i.e., well-managed ADHD) will be included except disorders that present a more severe group requiring treatment that might interfere with CBT (e.g., Major Depression, Oppositional Defiant Disorder).

C.8.c. Recruitment. The current recruitment strategy is intended to approximate the conditions under which *Anxiety Coach* would have the most impact, i.e. areas where psychiatric needs exceed mental health providers with specialization in CBT for childhood anxiety disorders. To maximize external validity the experimental treatment will be implemented by community therapists recruited from a large geographical area, particularly areas with a mental health shortage designation, and treatment will be paid for through traditional clinical mechanisms.[78] The principle limitation of the recruitment paradigm is that only patients with access to services will be included in the study. However, this study will establish the safety and efficacy of *Anxiety Coach* with differing levels of therapeutic contact before examining *Anxiety Coach* as a no contact treatment where it would be more difficult to address problems with safety, usability, or lack of progress. We anticipate that the data from the proposed study will prepare for future projects extending services to those outside the system by: a) improving the application; b) documenting the utility of *Anxiety Coach*; and c) creating a web-based portal

through which people in need of treatment could be followed by a provider with whom they have never had face-to-face contact.

C.8.d. Treatment Protocols. For Trials 2 and 3 the guidelines for each intervention instruct the therapist to interact (face-to-face or via the web-portal depending on the condition) once per week for 6 to 12 weeks. Although therapists are not given further instructions on how to deliver *TAU*, the six-session minimum will likely result in a higher level of care than is typically received in real-world settings, since standardization of contact across the interventions is necessary to examine the ability of *Anxiety Coach* to increase provider use of exposure.

C.9. Description of Assessment Measures. In Trial 1 therapists will complete study measures before training, two weeks after training, and then six months later. In Trials 2 and 3, all study measures will be completed at pre- and post-treatment assessment periods except as noted below. Independent evaluators under the supervision of Dr. Vickers Douglas blind to study condition will administer clinician-rated instruments. Therapist, parent and child report will be completed online via the Survey Research Centers electronic survey tools (or by paper and pencil and return via mail if completion electronically is not available).

C.9.a. Clinician-Administered Measures: Anxiety Disorders Interview Schedule for DSM-IV-Child Version Child and Parent Interview Schedules (ADIS-IV-C/P).[79] The ADIS-IV-C/P are structured interviews to assess the child's symptoms. Diagnoses reflect endorsement of symptoms as well as a severity rating (patient impairment/distress) of at least 4 on a 0-8 scale. The ADIS-IV will be administered in its entirety to the child and the parent together at pre- and post-treatment to determine whether an anxiety disorder is the primary diagnosis and the presence of comorbid diagnoses. Pediatric Anxiety Rating Scale (PARS).[80] The PARS is a summation of six items assessing anxiety severity, frequency, distress, avoidance, and interference and has been used as the primary continuous outcome measure in treatment studies.[30] Clinical Global Impression-Severity and Improvement (CGI-S/I).[81] The CGI-S/I is a 7-point clinician rating of severity of psychopathology and treatment response. The CGI-I will be completed at time 2 and youth receiving a score of 1 ("very much improved") or 2 ("much improved") will be considered treatment responders. Finally, the child and parents will be asked to rate the recent severity of the child's anxiety symptoms on a 0 to 10 scale.

C.9.b. Parent and Child Report Measures. Spence Children's Anxiety Scale (SCAS).[82,83] This scale measures anxiety symptoms in six areas that correspond with the anxiety disorders in DSM-IV. Child Sheehan Disability Scale (CSDS).[76] This scale allows the respondent to rate the degree of impairment in the child's and parent's social, school/work and family domains related to anxiety symptoms. Child Avoidance Measure (CAM). This scale allows the respondent to rate how much the child avoids things due to their fears and worries. Therapist Alliance Scale (TAS).[84] Affect toward the therapist (seven items) and perceived agreement with the therapist regarding tasks of therapy (one item) will be assessed at the end of treatment.

C.9.c. Parent Report Measures. Vanderbilt Assessment Scale (NICHQ) – Parent Informant. This scale is used to measure externalizing symptoms (i.e., ADHD and oppositional defiant disorder). Children's Accommodation Scale (CAS). This form is used to rate how the parent responds to the child's anxiety and distress. Depression Anxiety Stress Scale 21. Parent psychiatric symptoms will be assessed at screening and post treatment with the DASS21. Client Satisfaction Questionnaire-8 (CSQ-8).[87] Parent satisfaction will be assessed at the end of treatment with this self-report measure provided to the parent through REDCap survey. The modified System Usability Scale plus AC items (mSUSplus; Bangor et al., 2008; Brooke, 2013). Parents will complete the mSUSplus after treatment with anxiety coach.

C.9.d. Child Report Measures. Personal Health Question – 9. The PHQ-9 is a 9-item self-report measure of depressive symptoms over the previous two weeks. Child Automatic Thoughts Scale. This scale measures the frequency of self-reported anxiety provoking thoughts. Child Survey of Coping. This is a self-reporting measure of how the child copes with their fears and worries. Children will rate the severity of their anxiety symptoms on a daily basis using a 11-point scale on the iPod Touch. These report measures will be provided to the child through REDCap survey.

C.9.e. Therapist Report Measures. The survey, conducted under IRB 14-002608, will be an adaptation of the measures used in a previous study[15] and will inquire about demographic/practice information. Therapists will be asked to indicate whether or not they have used various interventions over the past 12 months with anxious children and adolescents (presented separately). Additionally, therapists will be asked about their beliefs about exposure. Therapists that provide study treatment will complete the exposure beliefs questionnaire again before and after treatment. The modified System Usability Scale plus AC items (mSUSplus; Bangor et al., 2008; Brooke, 2013). Therapists in all 3 trials will complete the mSUSplus. Therapist in Trial 1 will complete the SUS two weeks and six months after training. In Trials 2 and 3 therapists will complete the SUS as part of the post treatment measures.

C.9.f. Session Coding. All therapy sessions in the TAU and FTF-AC will be audio recorded and coded with a CBT for child anxiety Treatment Adherence scale that has been used in previous treatment studies, [18,67,74] in addition to recording the amount of time spent planning and conducting exposure. Audio recording will be used rather than video, as it will be easier to set-up and transport if exposures are completed outside of the office. Electronic communication between therapists and patients will be automatically recorded and phone conversations will be summarized in writing. These contacts will also be coded for recommendations regarding exposure. 10% of sessions will be coded by two evaluators independently to examine inter-rater reliability.

C.9.f.2 Electronic Data. All use of the Anxiety Coach system (desktop or mobile device applications) is automatically recorded. This data will include anxiety ratings, fear ladder items, and details on completed exposures. These data will be extracted to assess use of the system in all three trials. In all three trials therapists will be given a study name (i.e. T1therapist1) in the Anxiety Coach system. In Trial 1, therapist will be given access to Anxiety Coach for 1 year following the training. They will be free to use the system in their practice as they choose. Although the system is secure, therapist will be instructed that because it is in development that patient names should not be entered. As such, the system will automatically assign patient idenitifiers (e.g., Patient #1). In Trials 2 and 3, enrolled patients will be given a study name (i.e. T2patient1).

C.9.g. Therapist Support. The frequency and content of communication between the project director and therapists will be recorded. All electronic communication within Anxiety Coach will be automatically saved within the web-based portal and the duration and content of phone conversations or standard electronic communication will be logged.

C.9.h. Rater Training and Integrity. Clinician rated measures will be completed by independent evaluators (IEs) blind to the study hypotheses under the supervision of Dr. Vickers Douglas, who will ensure that evaluations are completed accurately and thoroughly. Therapy session recordings will be coded by a separate IE blind to the study hypotheses and assessment results. Dr. Whiteside will lead training of the independent evaluators in assessment and coding including ratings of criterion tapes and review of practice assessments. Raters will be expected to score within 15% of Dr. Whiteside's ratings on criterion cases. Dr. Whiteside will review 10% of assessments and session codings completed by the IEs in the beginning of the study and those whose scores fall outside of the 15% range will not conduct evaluations until this level of agreement is achieved. After competency has been established Dr. Whiteside will review 5% of assessments and sessions codings. Dr. Vickers Douglas will review assessment and coding discrepancies between the IEs and Dr. Whiteside during the study to reduce the effect of bias. All assessments done by the IE via videoconference will be audio recorded so Dr. Vickers Douglas and Dr. Whiteside can ensure that the evaluations are completed accurately and thoroughly.

C.9.i. Qualitative Measures. Dr. Vickers Douglas will work with Dr. Whiteside to identify questions and topics for a semi-structured interview script. The script will be pilot-tested to ensure that questions and follow-up probes are easily comprehended and delivered in a sensitive manner. The semi-structured script will follow guidelines for minimizing bias and increasing the reliability and validity of interview data.[90,91] The interviews will be conducted by an experienced qualitative interviewer not involved with the patients' medical care or development of *Anxiety Coach* or the treatment protocols. All interviews will be audio-recorded

C.10. Data Management and Statistical Considerations

C.10.a. Data Analytic Plan. Time has been budgeted for a Master-level statistician. The activities of the individual will be coordinated by the doctoral-level statistician dedicated to the Department of Psychiatry and Psychology under the ultimate direction of the Dr. Whiteside. The MS statistician will assume the primary responsibility of implementing the statistical analysis plan and completing standard statistical summaries of the study data. As this is a feasibility study and not powered to examine the statistical significance of group differences, the statistical analysis will be primarily descriptive in nature.

C.10.b. Tests of Specific Aims

C.10.b.1. Aim 1: Adapt *Anxiety Coach* for use with a health care provider. Data from an open trial of 15 patients treated with *Anxiety Coach* and the web-based portal in FTF-AC or MC-AC (7 to 8 per condition) will be analyzed descriptively. Quantitative data regarding adherence (accessing the application at least 50% of days) and improvement (symptom change) will be examined to ensure that patients are utilizing and benefiting from treatment. For qualitative data, themes regarding usability and treatment satisfaction will be identified and a coding strategy will be developed. Analysts with experience in qualitative data analysis will code interviews using methods of content analysis (i.e., systematic process of sorting and coding information based on themes).[92,93] QSR's NVivo 9 (QSR International, Doncaster, Victoria, Australia; NVivo 2010) qualitative data software analysis program will be used to facilitate data coding and sorting. The open trial will be monitored for adverse events, which will be addressed appropriately. Data from the therapist survey will be evaluated descriptively (i.e., frequency of endorsement of therapeutic strategies and attitudes toward exposure).

C.10.b.2. Aim 2: Assess feasibility, safety, acceptance, and impact of Anxiety Coach. Analyses for Trial 1 will consist of examining changes in therapist questionnaires via repeated measures analyses of variation and descriptively summarizing data on therapist use and ratings of acceptibility. Most appropriately for the present design of Trials 2 and 3, descriptive statistics will be calculated on all fidelity (e.g., frequency of exposure), feasibility (e.g., quantity and content of communication between the therapist and project director, frequency of assessing the application), and clinical variables (e.g., means, standard deviations, percentage of patients continuing to meet diagnostic criteria). Consistent with the ultimate goal of generating estimates of the effect of *Anxiety Coach*, symptom change within Trials 2 and 3 will be compared between groups using repeated measures analysis of variance (RMANOVA) and the frequency of the therapists' use of exposure will be compared between the TAU and FTF-AC condition using analysis of covariance (ANCOVA) to control for diagnosis and symptom severity. Given that this project aims to test the feasibility of a fully powered RCT, analyses testing group differences will be considered exploratory. Although the use of RMANOVA and ANCOVA has significant limitations (i.e., the treatment of missing data), the small sample size and inclusion of multiple therapists does not permit the use of a more powerful statistical approach such as a mixed-effects regression model. However, exploratory analyses using mixed-effects regression model will be conducted. These analyses will be completed to assist in planning design and analysis of a fully powered RCT, rather than to provide interpretable results.

C.10.b.3. Aim 3: Develop a protocol for implementing Anxiety Coach. To develop a protocol for using *Anxiety Coach* to increase therapist fidelity to evidence-based CBT and provide treatment with minimal direct contact, the frequency and timing of contact between the project director and therapists as well as the therapist and patient will be used to construct guidelines for monitoring and interacting with therapists and patients. The questions from patients and therapists will be summarized qualitatively and used to refine *Anxiety Coach* and develop the educational component of the protocol.

C.10.c. Attrition, Noncompliance and Missing Data. The intention to treat analysis set will serve as the principal analysis set. Attempts will be made to minimize the missing data due to missed visits (i.e., fewer than the required six appointments). To handle missing data the following approach will be used. The analyses of the primary outcome will be performed in two ways: 1) using complete case scenario i.e., those patients that

have data available on both time points and 2) imputing a rank from the earlier time point carried forward. Last rank carried forward has been shown to have better statistical properties than the last observation carried forward approach. In addition to these, we will also explore other sensitivity analysis such as imputation of a mean or median or worst or best case values in the respective groups. Findings from sensitivity analysis will be viewed in light of primary analysis prior to reaching final conclusions and interpretation of the results.

PROTECTION OF HUMAN SUBJECTS

4.1.1 Risks to Human Subjects

4.1.1.a. Human Subjects Involvement, Characteristics, and Design: Participants and their involvement will include: 1) community therapists responding to a survey, conducted under IRB 14-002608, of practice characteristics and beliefs during Phase I; 2) 30 community therapists receiving training and providing usability data in Phase II, Trial 1; 3) 40 therapists affiliated with institutions providing study intervention (Phase II, Trials 2 and 3); and 3) 75 children with an anxiety disorder ages 7 to 17 and one or more caregivers, anticipated to be up to 60 years of age, receiving study intervention (15 in Phase I, 60 in Phase II Trials 2 and 3). Children below the age of 7 will be excluded because they are deemed too young to safely and effectively engage with the study materials. There are no restrictions on ethnicity, social background, or gender. Study participation is entirely voluntary and participants may withdraw from the study at any time without penalty.

The inclusion of community therapists is necessary to characterize the state of community mental health and to test the feasibility of the study intervention for disseminating evidence-based treatment to community/non-specialty settings.

The inclusion of children with an anxiety disorder and a caregiver is necessary to examine the feasibility of improving treatment outcome for children with anxiety disorders. The project includes children, a special population, because this population is particularly at risk for not receiving evidence-based care and the project's aim is to improve access to cognitive behavioral treatment for childhood anxiety disorders. Children will be recruited through participating community therapists to maximize the external validity of the study as a test of the intervention's feasibility for improving care in community, non-research settings. Parents will provide consent for themselves and their child to participate. Children will provide assent.

4.1.1.b. Sources of Materials: Research material will be collected from the therapist survey respondents from IRB 14-002608, study therapists, child patients and their caregivers.

The information collected through the therapist survey materials will include demographics, frequency of treating patients with anxiety disorders, frequency of using a variety of therapy strategies, beliefs about exposure therapy, opinions regarding the usability of the application, and report of how often and why they chose to use the application. Reponses to the survey will be initially individually identifiable to allow recruitment of eligible therapists into Phase II. Only the staff at survey research center (SRC) will have access to this individually identifiable data, which will not be shared with the project researchers or other study staff.

Following consent, but prior to participation in Phase II Trials 2 and 3, eligible therapists will be asked to provide evidence of licensure with no disciplinary action. This information will be obtained by the study coordinator and will not be shared with other individuals including other study staff and researchers. Additional material will include therapist-provided audio recordings of treatment sessions that the independent evaluators use to code the therapists' use of treatment principles. The recordings will not be identifiable (i.e., they will be labeled with code numbers described below). The final material collected from therapists will include re-administration of the beliefs about exposures questionnaire from the survey in IRB 14-002608.

Material collected directly from the participants (child and caregiver) will be responses to behavioral ratings scales, psychiatric interviews, data entered into the Anxiety Coach application, and session content from audio recordings. The therapy sessions will be recorded by the therapists, transferred to the study team via the secure intervention web-portal, labeled with a code number (see below) by the study coordinator, and coded by the independent evaluators. All other data will be collected and entered by the independent evaluators.

Appropriate steps will be taken to ensure the confidentiality of data from survey respondents, study therapists, patients, and parents. To begin with, participants (therapists, patients, and caregivers) will be assigned study codes that are not based on the individual's information. All written, electronic, and audio recording material and data will be identified only by code. The key linking participants to study codes will be kept in a locked cabinet separate from the data. All paper-generated data will be stored in locked files in the office of Dr. Whiteside. All computer-generated data will be maintained in password-limited, secure network drive files. All identifiable information from the survey will have the same level of protection with the addition of being managed by SRC and not made available to the study staff. To protect patient confidentiality, only

authorized persons at Mayo Clinic and the Institutional Review Board will have the right to review research records. Confidentiality of those records will be protected to the extent permitted by law. Research records will be kept separate from identifying information in a locked cabinet and will not be released without the participant's consent unless required by law. Identifying information will be removed prior to publication and presentation of the study results. The Anxiety Coach application will not have any fields that request identifiable in Phase I or II, Trials 1, 2, or 3.

4.1.1.c. Potential Risks: The risks of participating in this project are considered to be minimal and include completing relatively lengthy research measures, the potential to be randomized to a condition with less effective treatment, and breach of confidentiality. The methods to address these potential risks are outlined below in Section 4.1.2.b.

One potential risk of participating in this project includes discomfort during the data collection (survey, phone screenings, and assessments) related to discussing sensitive topics and the length of the evaluation. However, the length of material completed by therapists are minimal and the patients in the study are seeking treatment and presumably are interested in discussing their symptoms with an expert clinician. It is estimated that the survey will require 20 to 30 minutes to complete, and the patient interview and questionnaire completion will take approximately 2-3 hours for the initial evaluation and 1-2 hours for the post-treatment assessment. Having the family complete questionnaire packets at home where the family can work at their own pace and take breaks will minimize the burden associated with lengthy assessments.

Although difficult to predict with certainty, the degree of risk and benefit may differ among the three conditions. Neither the relative benefit of augmenting face-to-face therapy with *Mayo Clinic Anxiety Coach* nor the relative risk of minimal contact treatment have yet been tested, and so the relative cost-benefit ratios are uncertain. The risk of being randomized to TAU is that the patient may receive a potentially less effective treatment. However, as this treatment is the standard intervention outside the study, participation in the study will not have a detrimental effect on the quality of the patient's treatment. In fact, the study requirement of a minimum of 6 sessions will likely result in a higher level of care. Further, there is no portion of the study during which patients will be asked to receive no treatment. Alternatively, patients in the minimal contact *Anxiety Coach* condition may be at risk of receiving a less effective treatment because of the decreased therapist contact. However, the goal of the study is to examine the feasibility of minimal contact treatment. Thus, patients may receive emergent care or more frequent contact if needed. Such occurrences will be collected as measures of tolerability. Within all conditions if additional care is clinically indicated the therapist (with the assistance of the study staff under the direction of Dr. Whiteside) will assist the family in making arrangements for appropriate care.

More generally, the study includes potential risks related to psychotherapy. In rare cases psychotherapy may exacerbate symptoms. Should a patient's symptoms increase significantly anytime during the study and require discontinuation of study treatment, families will be connected with appropriate alternative treatments outside the study protocol including psychotropic medication, additional psychotherapy, or hospitalization. In addition, as with all treatment, the therapists will closely monitor the patient's emotional well-being and pace therapy appropriately (i.e., recommending a slower pace or "exposure breaks"). The therapists will also monitor parent-child interactions and the parent's emotional state to determine if further action is indicated. Moreover, the study therapists will have access to the intervention specialists in all conditions as an additional resource for protecting patients against harm.

The confidentiality of therapists, in addition to patients (children and caregivers), will be maintained through the procedures described above in Section 4.1.1.b. To minimize risk, identifiable information from the survey will only be available to the SRC. However, therapist's inclusion in the pool of providers eligible for participation in Phase II implies an endorsement of openness to CBT and infrequent use of exposure. However, this is thought to pose a limited risk as previous research suggests such responses will be the norm. During recruitment, the structure of phone screenings will allow therapists to decline participation in a manner that does not imply a history of disciplinary action.

4.1.2 Adequacy of Protection Against Risk

4.1.2.a. Recruitment and Informed Consent: Recruitment will begin with a survey sent to all mental health providers contracted by MMSI conducted under IRB 14-002608. The survey will include consent language approved by the Institutional Review Board and require the participant to actively indicate understanding and willingness to consent. Recipients will be able to decline participation and indicate that they do not wish to be contacted again (i.e., the follow-up to nonresponders). The SRC will provide a de-identified data set to the study team who will identify all eligible participants. The SRC will provide the name and contact information for a randomly selected recruitment pool of 80 therapists (or more if needed), but not the associated code numbers. During the screening phone call placed by the project director, the study will be described (including inclusion criteria) and the therapists will be invited to participate. Those interested will have the consent form reviewed and be mailed two copies (one to return, one for their records). Only after one copy of the written consent form has been received will the study staff verify that the therapist is licensed and does not have a history of disciplinary action. Therapists will then complete appropriate research ethics and HIPAA training.

Patients (children and caregivers) will be recruited for participation in the study by the enrolled therapists. During the initial evaluation the therapist will describe the study including its voluntary nature using a prepared script. The therapists will provide families that express interest in participation a study packet and encourage them to contact study staff to schedule screening visit. The study coordinator will conduct a phone screening with the caregiver including questions to assess the presence of an anxiety disorder and obtain other information relevant to inclusion and exclusion criteria (e.g., diagnostic and treatment history). Those who are determined to be ineligible will be offered other treatment options including treatment with the referring therapist, an evaluation at Mayo Clinic outside of the study if appropriate, and resources for finding other providers. Those who appear to be eligible will be scheduled for the videophone Consent and Evaluation visit. During the initial part of this visit, the patient and parents will be given a review of the informed consent document including information about the treatment options within the study, potential risks and benefits of study participation, as well as any alternatives to participating in research. The investigators will try to foster an open exchange of information and will encourage the child and caregivers to ask questions and discuss concerns. It will be the responsibility of Dr. Whiteside to ensure that all participants (therapists, patients, and caregivers) have provided consent/assent and understand their role in the research. Participants will be told that they can discontinue participation at any time, or refuse to answer any study questions, without adverse consequences. If patients and caregivers are interested in participation, a copy of the consent and assent documents will be signed and placed in the postage-paid envelope included with the study packet. To minimize delay in beginning therapeutic treatment, the pre-treatment evaluation will be conducted at this visit. However, patients will not be considered to be enrolled in the study until the signed consent/assent documents have been received and signed by study staff. In the event that data is collected but signed consent/assent documents are not received, data will be excluded from any research-related activities or analyses. Data on screening, eligibility decisions, and enrollment will be tracked.

4.1.2.b. Protections Against Risk:

At the time this application was submitted the Research Committees within the Department of Psychiatry and Psychology and the Department of Pediatrics with Mayo Clinic approved all study procedures including the language in the consent and assent forms to ensure that it is simple and understandable. Prior to the onset of the study, the Mayo Clinic Institutional Review Board will also approve these materials. The research team will carefully protect the confidentiality of all participant research information. Investigators are required to undergo and periodically renew training in research ethics and HIPAA. Given their role in recruiting patients, participating therapists will complete similar training for that role. All paper-generated data, computer-generated data, and session recordings will be labeled with code number unrelated to the patients' identifying information. All paper-generated data will be stored in locked files in the office of Dr. Whiteside or the SRC. All computer-generated data and session recordings will be maintained in password-limited, secure network drive files. Participant names (or other identifying information) will not be kept on the study measures. Instead code numbers will be used and the key linking code numbers with participant identifiers will be kept in locked files separately from the data. Only Dr. Whiteside and the study coordinator (or the SRC for survey data) will have access to the code key. To protect the confidentiality of data collected through the Anxiety Coach application no-identifiable information will be requested. Specifically, rather than requesting full names and birthdates, the system will generate identifiers (e.g. Patient #1) rather than names and allow entry of ages but not birthdates.

The in system messaging capabilities have reminders not to include identifiable information. Patients will be required to agree to the Anxiety Coach Terms of Use that explains what data Mayo Clinic collects and how that data is used. The Terms of Use will inform patients that they have the ability to decline to have their data used for research purposes.

To decrease the likelihood that therapists or families feel coerced to remain in the study or feel it was not worth their investment of time and effort the staff will approach informed consent as a continuous process by: setting clear initial expectations about the research study, routinely assessing participant (patient and therapist) comfort with the study, reviewing the study components that have been completed and that are upcoming at each evaluation time point, supporting non-billable therapist time to manage patients electronically, reimbursing participant families for their time to complete study assessments, and allowing participants (patient and therapist) to keep an iPod Touch. To decrease the likelihood that youth will feel coerced by their parent to participate, the IE who completes the enrollment assessment will directly ask the child if s/he is interested in participating. If the IE has concerns about that the child is feeling coerced he will ask to speak to both the child and the parent individually to gather further information, and then discuss his/he concerns with the PI. If patients deteriorate or develop clinical crises the investigators may recommend adjunctive treatment or study termination. Prematurely terminated participants may continue with study treatment and provide assessment data. All participants randomized to treatment conditions will be included in data analyses and the circumstances surrounding missing data will be recorded.

Thorough screening and assessment will aim to rule out psychiatric conditions in children and caregivers that may prevent families from participating in the study. Once in the study families will be followed closely by a therapist and an intervention specialist with considerable experience providing treatment for childhood anxiety disorders under the supervisor of Dr. Whiteside. Dr. Whiteside, the treating therapist, an intervention specialist or a covering clinician through the Mayo Clinic Division of Child Psychiatry and Psychology will be available for research subjects 24 hours a day, 7 days a week. Side effects and adverse events will be monitored closely throughout the study. Specifically, the therapists (or evaluator) will conduct a general inquiry at each contact regarding symptomatology, adverse events, self-harm, or any health complaints. If at any point during the study participants develop elevated risk for harm to self or others, or experience increased symptoms, appropriate treatment will be instituted. Reported complaints will be coded on a standardized form as Mild (minor complaint causing no interference and not requiring intervention), Moderate (more than minimal problem, source of some interference and may require intervention), Severe (significant complaint, definite interference requiring intervention), or Serious (life threatening, a potential for long-term disability, and/or requiring hospitalization). Based on the nature of the complaint the independent evaluator will determine whether it is related to the study, and Dr. Whiteside will take appropriate action (e.g., monitoring, adjunctive intervention, removal from study). Any cases of suspected abuse will be reported consistent with the roles of mandated reporters by the therapist and study staff in conjunction with Dr. Whiteside. Any instances of suspected malpractice by study therapists will be addressed consistent with institutional guidelines, the ethics code of the American Psychological Association, and the credentialing body of the therapist in question.

Protections related to subjects with depression or suicidal ideation are as follows: Patients who endorse severe depression or suicidal ideation during the screening phone call or the initial evaluation will not be enrolled in the study. Patients who endorse mild to moderate depression that is secondary to a primary anxiety disorder during the screening, initial assessment, or post-treatment assessment will be allowed to participate in the study. In all cases of severe or moderate depression, the project director will communicate the results of the patient's depression evaluation to the treating therapist. If during any contact the patient is determined to have active suicidal ideation, appropriate steps will be taken by the project director, Dr. Whiteside, and/or the treating therapist to ensure the patient's safety, i.e. emergent evaluation or hospitalization. The PI (Dr. Whiteside) is a board-certified child psychologist with extensive experience treating youth with anxiety disorders, including comorbid suicidality. Dr. Whiteside will follow standard policies and procedures developed by the Mayo Clinic Child and Adolescent Division in the Department of Psychiatry and Psychology, e.g., comprehensive assessment of depressive symptomatology, assessment of suicidal ideation (inclusive of intent, means, plan), immediate notification to the subject's legal guardian, and referral to the Mayo Clinic Child and Adolescent Inpatient Psychiatry unit (in cases of immediate lethality). Implementation of strategies to

mitigate suicidal behavior will be tailored to the specific presenting case. If necessary, additional services, or inpatient treatment will be made available but are not provided by the study.

To address clinically-related crises that may occur during a clinical trial the Adjunct Services and Attrition Prevention procedures and guidelines will be followed, based on an adaptation of the MTA's procedural manual (ASAP)[94] similar to other NIMH clinical trials (e.g., MTA, POTS). Under ASAP guidelines situations that require interventions will be addressed in a manner that responds appropriately to the emergent clinical needs of the participant families, while, to the extent possible, maintaining the integrity of randomization (i.e., preventing attrition), and limiting contamination of study treatments. This approach is adopted to maintain subjects in the study and intent-to-treat analyses.

In cases where children are receiving anxiety-related medications prior to the period of study eligibility, or where initiation (or discontinuation) of a medication during the study period seems clinically necessary, this care will be managed by prescribing physician. Although we expect that medication changes will be minimal or absent, if such occur, we will analyze outcomes from patients with and without medication changes occurring during the course of the study to determine if changes in outcomes are attributable to medication changes.

4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

Participants in the study potentially will benefit from receiving a comprehensive psychiatric evaluation and treatment for childhood anxiety and access to a novel treatment aide (either during or after the study period in the treatment as usual condition). Although this study is designed to develop the treatment, rather than demonstrate efficacy, participants will likely experience improvement in symptoms and functioning. In addition, the patients will be compensated $25 for pre-assessment and $25 for post-assessment (total of $50) and the therapists will be compensated up to $75 per patient, up to 3 patients. The patient and therapist will be able to keep the iPod Touch. Benefits to others are discussed in Section 4.1.4.

4.1.4 Importance of the Knowledge to be Gained

The primary benefit to society is the creation of a novel tool for 1) disseminating evidenced-based treatment for childhood anxiety disorders to practitioners and 2) providing effective care to children who have limited access to brick and mortar mental health facilities. Anxiety disorders are the most common psychiatric disorders in childhood with prevalence rates as high as 15%, but the least likely to be treated (approximately 30%).[1-4] If left untreated or inadequately treated, these disorders cause substantial impairment across a variety of domains of functioning, are highly co-morbid with other disorders, and often persist into adulthood.[5-8] In addition to improving the lives of children with anxiety disorders and their families, increased access to treatment has a benefit for society as a whole by decreasing the health-related costs of anxiety disorders.

Although a wealth of data supports the efficacy of cognitive behavioral therapy (CBT) for childhood anxiety disorders,[30,49-51] efforts to transport these interventions into clinical settings have been largely unsuccessful.[18,52-54] The poor performance of efficacious interventions in clinical settings is likely due to the infrequent use of exposure.[14,15] The low rate of exposure stands in stark contrast to the emphasis on this procedure in manualized treatments and the general scientific consensus regarding its importance.[29,55-58,61,62] By developing a tool for disseminating and providing CBT with minimal direct contact, the current study will increase access to evidence-based care for children who have previously been deprived of effective treatment. More broadly, the tools developed in this proposal may be adapted to increase the efficiency, generalizability, and durability of treatment for other psychiatric disorders.

The mobile device-based treatment and supporting protocol will be considered the products of this grant. To date, no such application with data supporting its effectiveness exists to disseminate or provide CBT with minimal direct contact for childhood anxiety disorders. By completing the pilot RCT in Phase II and revisions in Phase III, the investigators will be well-positioned to pursue funding for further evaluation of the treatment. This line of research has the potential to inform research into the development of similar approaches for other psychiatric disorders. To maximize the translational value of the current study the scientific results and the treatment protocol will be prepared for publication. In addition, the data gathered from this project will form the basis of an application for R01 funding to investigate the efficacy and cost-effectiveness of the intervention in a fully powered clinical trial.

4.1.5. Data and Safety Monitoring Plan

The treating therapist, an intervention specialist, and Dr. Whiteside will closely monitor participants once they have been enrolled in the study. Therapists will monitor patient symptoms and safety as part of clinical care through face-to-face sessions or the web-portal depending on the condition. The therapists and intervention specialists will review the patient progress and safety on a weekly basis through the daily ratings available in the web-portal. Dr. Whiteside will supervise all study activity and be responsible for all data and safety monitoring. Monitoring will consistent of weekly meetings with intervention specialists, independent evaluators, and the project director to review all active participants and data collected via telephone screenings, assessments, the web-portal, session recordings, and therapist reports. All adverse events will be reviewed and reported by Dr. Whiteside with the assistance of the project director to the IRB. The IRB will also monitor data and safety through annual progress reports. Drs. Whiteside (with consultation from Drs. Abramowitz, Ollendick, and Andersson) will review data at the end of the open trial and pilot RCT to assess the appropriateness of each treatment and review any adverse events. As noted in Sections 4.1.1.b. the confidentiality of research data will be closely guarded through separating identifying information from patient responses and storing all data in locked or password protected locations. Dr. Whiteside has overall responsibility for monitoring the integrity of the study data and patient safety under the oversight of the IRB. Dr. Whiteside will be responsible for reviewing and reporting to the IRB plans for data and safety monitoring, reviewing adverse event reports, monitoring data integrity during the study, and interpreting the relevance to the study of any external scientific or therapeutic developments.

The following procedures will be followed to ensure participant safety: a) Participants at increased risk for adverse events will be excluded from the study (e.g., actively suicidal, psychosis, below age 7); b) Participants' symptoms will be closely monitored throughout the study by the treating therapist, intervention specialists, and Dr. Whiteside; c) Participants will be offered additional, emergent treatment as needed; d) the study staff will meet weekly to discuss participant safety; and e) The adequacy of safety procedures and the safety of participants will be monitored by the IRB.

The following procedures will be followed in reporting adverse events: All adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Serious Adverse Event (USAE) will be recorded on the appropriate case report form. Records of these events will be maintained and reports submitted to the IRB according to the regulatory requirements. Expected serious adverse events (SAEs) and nonsignificant (not serious) adverse events (AEs) will be reported to the IRB at the annual review. Expected adverse events and anticipated adverse device effects are those listed in the protocol, investigational device information, or consent documents as a potential risk factor. USAEs will be reported to the IRB within five working days of learning of it using the Reportable Event form in the IRB electronic system.

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