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Protocol

Psychotherapy for Anxiety in Children with Autism Spectrum Disorder (TAASD)

Abstract:

Autism spectrum disorders (ASD) are common neurodevelopmental syndromes affecting 1% of U.S. children. Comorbid anxiety disorders affect 40 to 50% of children with ASD, causing substantial distress and impairment over and above that caused by ASD alone. High anxiety is associated with increased severity of ASD symptoms and social maladjustment in affected youth. Further, parents of children with ASD consider anxiety-related problems to be among the top two challenges facing their children. Although standard practice cognitive-behavioral therapy (CBT) has been established as an efficacious and safe treatment for anxiety disorders among typically developing youth, its utility in comorbid cases with ASD remains unknown. To date, no studies have experimentally compared standard practice CBT to a cognitive-behavioral intervention that has been personalized for children with a comorbid presentation of anxiety and ASD. Accordingly, we are proposing a randomized controlled trial (RCT) to be conducted at three treatment sites to evaluate the efficacy of personalized CBT for anxiety in ASD (Behavioral Intervention for Anxiety in Children with Autism: BIACA) relative to standard practice CBT for anxiety (Coping Cat program). Furthermore, this study will employ a treatment as usual control group to assess the efficacy of each CBT arm relative to the normal treatment (i.e., a Treatment As Usual control group). The proposed research will: (1) examine the efficacy of BIACA relative to Coping Cat, which represents standard practice treatment, and the efficacy of both these treatments relative to a treatment as usual (TAU) control group, (2) evaluate the maintenance of treatment gains, (3) examine the impact of personalized intervention on functional outcomes such as social responsiveness, loneliness, and playdate quality, (4) test autism severity as a moderator of treatment outcome, and (5) explore other moderators and mediators of treatment outcome. Youth (ages 7-13 years) with ASD and co-occurring anxiety will be randomly assigned to one of the three conditions: BIACA, Coping Cat, or TAU. Considering the rising number of children diagnosed with ASD together with the frequency and severity of comorbid anxiety, the proposed work is tailored to the unique needs of youth with ASD and will provide a timely contribution to public health efforts.

Background and Significance:

Affecting as many as 1 in 88 children (1 in 58 boys) in the United States, ASD is an increasingly common childhood neurobiological condition.[1-5] Anxiety disorders are common and impairing among children with ASD. As many as 50% of youth with ASD have ≥1 diagnosable anxiety disorder. Generalized anxiety disorder affects at least 35% of those with ASD; separation anxiety disorder affects at least 38%; obsessive-compulsive disorder (OCD) affects at least 37%; and social phobia affects at least 30%.[6-9] Clinically significant anxiety is associated with functional impairment and poor outcomes in youth with ASD.[10-13] The relative frequency of clinical anxiety among children with ASD indicates that anxiety is an important treatment focus,[14, 15] with parents rating it as the second biggest problem for youth with ASD.[16]

Clinical anxiety is linked with significant functional impairment in youth with ASD. For example, higher parent-rated child anxiety is associated with greater impairments in social responsiveness[11] and social skills[10] in youth with ASD. This follows from the tendency of social anxiety to promote social avoidance, which prevents opportunities for the development of relationships.[17-19] In individuals who already have social skill deficits, social avoidance likely adds an additional barrier to friendship and acceptance.

Additionally, several large studies of children with ASD have found strong linkages between clinical anxiety and increased severity of ASD symptoms, such as repetitive behaviors[11], sensory symptoms[20], and total ASD symptoms,[21] even when controlling for intellectual impairment, social maladjustment, and degree of speech impairment. It is therefore possible that treatment of anxiety could positively impact core ASD symptom severity.[22]

Clinical anxiety is a valid treatment target among children with ASD based on emerging genetic, psychophysiological, and psychometric evidence. First, Gadow et al. demonstrated in genetic linkage studies that several genetic markers linked with anxiety disorders in typical populations are also linked with anxiety in children with ASD[23-28]. Second, emerging evidence from startle paradigms has demonstrated a linear relationship between physiological arousal in response to stressors presented in the laboratory and anxiety symptoms exhibited by children with ASD, demonstrating the same biomarkers for anxiety shown by typically developing children.[29] Recent fMRI data indicate that higher social anxiety in patients with ASD is associated with greater activation of the amygdala in response to presentation of faces showing negative affect, consistent with findings in typical patients with anxiety.[30] In addition, anxious/depressed symptoms in youth with ASD were associated with total and right amygdala volume, suggesting a brain-behavior relationship in which abnormal amygdala functioning in ASD could contribute to increased risk for anxiety.[31] Third, psychometric data on anxiety symptoms in youth with ASD show a convergent, concurrent, and discriminant validity for diagnostician-, child-, and parent-reports of anxiety symptoms which separate from autism symptoms per se. Fourth, we have published a conceptual model[32] of the origin and impact of clinical anxiety in ASD. Individuals with ASD experience frequent autism-specific stress (e.g., social confusion; prevention of access to preferred activities during school), likely increasing negative affectivity—a consequence of stress.[33] Under conditions of heightened negative affect, children often develop focal anxiety symptoms.[34] This heightened anxiety triggers: (1) a pattern of avoidance caused by negative reinforcement that impairs functioning (e.g., social and schoolwork avoidance) and (2) maladaptive coping responses (e.g., increased repetitive behaviors) that distract from the anxiety. Given the emerging evidence of the biological and statistical validity of clinical anxiety in ASD, and the well-documented association between anxiety and social and other functional impairment in ASD, anxiety is a noteworthy treatment target in this population.

CBT treatments have produced medium to large effect-size improvements in anxiety in typically developing youth.[35-38] The Child/Adolescent Anxiety Multimodal Study (CAMS) CBT condition yielded a positive response rate on the CGI-Improvement scale of ~60%, more than doubling the placebo response.[35] Anxiety reduction achieved through CBT has been associated with reductions in functional impairment.[39] However, most trials that have established the efficacy of CBT have excluded children with ASD given the unique set of needs in this cohort. Work from our group suggests that children with moderate autism symptoms were significantly less likely to improve than typically-developing children in standard practice CBT for anxiety. The odds of a child with moderate autism symptoms responding to standard practice CBT were 6.42 times less than that of a typically developing child.[40] Accordingly, it is unclear whether the powerful treatment effects associated with standard practice CBT can be attained in the treatment of anxiety disorders seen in children with ASD. Well-designed studies of CBT for OCD[41-43] have also found impressive outcomes.

Several exploratory trials offer initial evidence of possible efficacy of CBT for anxiety in ASD. Wood et al. conducted an exploratory clinical trial[44] of an individualized CBT developed for children with ASD that employs a modular treatment algorithm, with similar aged youth (N=40) randomized to CBT or a waiting list. Children randomized to CBT had primary outcomes comparable to those of CBT for typically

developing children with anxiety disorders,[35, 36] with large effect sizes for most outcome measures. The modular CBT program was superior to a waitlist control in response rate (76.5% vs. 8.7%); remission rate (52.9% vs. 8.7%); clinical severity (d=2.5); and Social Responsiveness Scale scores (d=.75).[22, 44] Storch et al. recently completed a randomized controlled trial (N=45) of the Wood CBT protocol relative to treatment as usual (TAU) in youth with ASD and comorbid anxiety. Significantly more youth responded to CBT (18/24) versus TAU (3/21) with an effect size on the PARS[45] of d=1.42.[46] In Drs. Wood and Storch's NIH-funded trial of CBT for adolescents with ASD and anxiety, significantly more youth responded to a revised version of the Behavioral Interventions for Anxiety in Children with Autism (BIACA) manual (15/19) relative to a waitlist control (3/16).

Group therapy formats have been used in four pilot trials that have also shown benefits.[47-50] Limitations of these studies included a lack of independent ratings of outcomes, no assessment of treatment fidelity, non-modularized treatment format, and in one case, a lack of random assignment. While efficient, the linear format of group therapy limits matching intervention techniques to patient characteristics. Given the heterogeneity of phenotypes in ASD, individual interventions (e.g., modular treatments) tailored to a patient's specific characteristics, such as the one used in the proposed trial, are likely to be particularly efficacious.[51] Collectively, these studies suggest that personalized CBT for anxiety in youth with ASD is a promising modality, though the preliminary nature of the studies precludes conclusions about its efficacy and about its relative efficacy compared to standard practice CBT**.**

School-aged children with high-functioning ASD have cognitive assets that could facilitate response to CBT that is tailored to their clinical presentation. Children with high-functioning ASD are described as being "very verbal" and have average to above-average cognitive and language abilities.[52] Studies of information processing and cognition in high-functioning ASD suggest wide variation in children's capacity for abstract reasoning.[53, 54] CBT elements that are designed to support concept formation and generalization, and that are delivered in a developmentally-appropriate manner, could be accessible to affected youth.

As evidenced by our pilot work,[44] we have expanded traditional anxiety-focused CBT models to address the ASD-related clinical characteristics (e.g., poor social skills) that may exacerbate anxiety symptoms or render them less treatable.

Poor social functioning is a key autism-related deficit that requires treatment in CBT for anxiety in ASD. About 80% of children with ASD and anxiety in the Wood et al.[44] trial met criteria for social phobia. Children with ASD and high social anxiety are doubly impacted: they have core social deficits related to ASD (e.g., impaired conversation initiation and maintenance) as well as a debilitating fear of rejection that is associated with social maladjustment in ASD.[10] The typical CBT exposure to address social anxiety involves engaging with others in increasingly challenging social situations, which typically reduces fearful avoidance. However, without social skills to compensate for ASD-related social deficits,[55] exposures are less likely to succeed because unskilled, counterproductive social strategies are likely to be used, making unsatisfying and potentially humiliating social interactions a likely outcome, thereby promoting anxiety rather than reducing it.

Because traditional social skills training approaches often do not generalize to children's daily environments[56], we employ an alternative model. Informed by Brewin's memory retrieval competition model, our personalized CBT program builds compensatory social skills (e.g., offering guests' choices) coached by parents "in the moment" in naturalistic settings (cf. the pivotal response technique of priming).[44, 57-60] To enhance skills retention and generalization, targeting home and school social settings is

important: (1) carefully planned play-dates coached by parents offer a controlled arena within which to practice skills that increases the chances of success, promoting friendship development;[44, 55] (2) empathic peer volunteers at school can be trained to include target children with ASD in their conversations, giving children an opportunity to participate in the most relevant of social settings with reduced difficulty level and, consequently, a higher chance of success.[44, 61, 62] During CBT sessions, reflective discussions about these social experiences can bolster insight into complex social phenomena (e.g., a playmate's perspective).[58, 63] These treatment elements incorporate both the encoding specificity principle (through the inclusion of peers in relevant settings) and deep semantic processing (i.e., reflective discussions) to promote memory retrieval and application of skills.

Repetitive behaviors can interfere with the development of positive peer relations.[64] Circumscribed interests and stereotypies associated with ASD may prevent children from experiencing rewarding peer interactions because they engender rejection. Standard CBT interventions do not address these symptoms. However, habit reversal[65] and operant procedures[66] are promising techniques that we have adapted to reduce manifestations of circumscribed interests and stereotypies during peer interactions.[58, 60, 63]

Moderators of treatment effects help answer the question "What treatment works best for which patient?" [67] Kraemer has argued that clinical trials primarily powered to test treatment efficacy can play an important role in generating hypotheses about patient subgroups that may respond better to specific treatment modalities.[68, 69] Moderator variables are initially based on empirical precedent, theory, and logic. A number of pediatric clinical trials for depression have found that baseline symptom severity moderates outcome (e.g.,[70, 71]). In a recent study, Puleo and Kendall[40] found that autism symptom severity in typically developing children moderated treatment response in standard CBT versus family-based CBT. A similar relationship is expected in the present trial. For example, greater ASD symptom severity (e.g., social communication impairments) may be a hindrance to optimal response to standard CBT. In comparison, personalized CBT for anxiety in ASD (BIACA) uses ASD-specific adaptations and collateral supports to overcome ASD-related challenges. Thus, the more prominent a child's ASD symptoms, the more we expect BIACA to differentially impact treatment outcome in comparison to standard CBT.

The present trial will explore mediation.[68] This trial recognizes a synergy between anxiety and autism symptoms in children with ASD.[32] Therefore, it is of considerable importance to explore whether treatment-related reductions in anxiety mediate improved autism symptoms, and, complementarily, whether treatment-related reductions in autism symptoms mediate improved anxiety. Because anxiety is considered both a product of autism-related stress (e.g., social confusion) as well as a trigger of exacerbated autism symptoms that serve as a maladaptive coping response (e.g., social isolation, repetitive behaviors),[32, 40] it follows that improvements in the affect domain might beget improvement in autism symptom severity, and vice versa.

The considerable mental health need among children with ASD and clinically distressing anxiety is a widespread problem in need of attention. The proposed project advances the field by providing a rigorous test of efficacy of personalized CBT for anxiety in ASD against standard practice CBT for anxiety by addressing the following: (1) The study will be adequately powered to test the primary and secondary hypotheses. By employing a condition that represents standard CBT (i.e., Coping Cat), the study will answer the question of whether CBT personalized to the needs of youth with ASD and anxiety outperforms standard CBT.[72, 73] (2) The trial will include multi-method outcome measurement, including measures of anxiety valid in ASD samples, and measures of functioning independent of anxiety severity.

(3) An a priori moderator will be tested, and other moderators will be explored. (4) A multisite plan, with therapy supervision provided by study personnel other than PIs/treatment developers, provides information on the portability of treatment and enhances generalizability of findings.

Specific Aims:

Aim 1: To evaluate differential change over time in anxiety symptoms and response rates for the treatment conditions compared to each other and relative to a treatment as usual (TAU) control group.

Aim 2: To examine the durability of treatment gains for youth who are deemed as treatment responders.

Aim 3: To identify patient factors that are linked with differential treatment response such as the interaction between treatment condition and ASD severity on outcome measures post-treatment.

Aim 4: To explore whether treatment reductions in anxiety mediate improved autism symptoms and whether treatment related reductions in autism symptoms mediate improved anxiety

Research Plan:

Overview

The proposed investigation is a multi-site RCT comparing CBT that is personalized to youth with ASD and anxiety to standard practice CBT in youth (aged 7-13 years) with ASD and clinically significant anxiety. We will randomly assign patients after screening to a CBT intervention for anxiety in ASD (BIACA) versus standard CBT for anxiety (Coping Cat) versus treatment as usual (TAU*)*. The BIACA manual is personalized for anxiety in youth with ASD and has been designed in our pilot clinical work,[44, 46] and will be used across sites. Similarly, the Coping Cat CBT program is manual-based, has been supported in past NIH RCTs,[35, 37, 38] and will be used across sites to represent standard practice. Those in the TAU condition will refrain from active treatment for 16 weeks. Assessments will occur at Screening, Mid-treatment, Post-treatment and 6-month Follow-up.

Participants will include children and their parents recruited using a procedure designed to ensure that participants evidence clinically significant anxiety at the start of treatment in addition to their ASD diagnosis. Parents will be given a 20-minute telephone screening to elicit preliminary inclusion/exclusion information. The screening assessment determines "caseness" (formal presentation of the informed consent agreement, clinical assessment). Child- and parent-report forms will be completed at this visit.

Inclusion/Exclusion Criteria

Inclusion criteria:

(1) Outpatient boys and girls with ASD (see below) between the ages 7-13 years at consent.
(2) The child meets cut-off criteria for ASD as determined by scores from the Childhood Autism Rating Scale-Second Edition[74], the Autism Diagnostic Observation Schedule-Second Edition[75] and a consensus from PI's across sites about the child's diagnosis.
(3) The child meets criteria for clinically significant anxiety symptoms as defined by a minimum score of 14 on the PARS Severity Scale and a minimum anxiety severity score of 3 on the CGI-S.
(4) The child has a Full Scale and Verbal Comprehension IQ>70 as assessed on the WASI [76]. This level of intellectual ability is frequently used to demark the boundary of "high functioning" ASD, and we and

others[47, 77] have adopted this in our CBT trials for children with ASD to achieve acceptable external validity.

(5) Participants with comorbid depression, tic disorder or disruptive behavior disorders will be acceptable as long as the anxiety symptoms are considered the primary mental health problem (i.e., most impairing/distressing) after ASD. As with our IQ criteria, this entry criterion is reflective of the ASD population, which tends to have multiple comorbidities (in our pilot trials, children had an average of 4 comorbid disorders, and the majority met criteria for ADHD),[44, 46] and represents an effort to balance internal and external validity by including a representative sample of children with ASD and anxiety while preserving the integrity of the RCT. (a) Eligibility will be guided by the following principle: For participants presenting with comorbid symptomology, the comorbid conditions cannot be sufficiently severe to warrant immediate treatment or require ongoing medication titration. (b) Each potential participant will be discussed on the weekly cross-site SC calls and agreement across sites will be required for study entry. To determine principle diagnosis, the assessing clinician will determine if any non-anxiety disorders are present through the ADIS-IV. In the instance of co-morbid diagnoses, the clinician will establish which diagnosis is most impairing/distressing. A consensus panel consisting of the PIs and clinician will be used for more complicated cases.

(6) Stable psychiatric medications will be allowed if the dose has been stabilized and the family and psychiatrist affirm no plan to alter the dose or change medication in the foreseeable future. See exclusion criterion below regarding psychiatric medication. The majority of children with ASD (aged 8-13) have been prescribed psychiatric medication.[78, 79]

Exclusion criteria:

(1) Receiving concurrent therapy targeting anxiety, social skills training with homework, or behavioral interventions (e.g., applied behavior analysis). Families will have the option of discontinuing such services to enroll. This excludes academic tutoring, occupational therapy, speech therapy, school counseling that is no more than 60 minutes per week in duration, school aides, and social skills training groups that do not include homework and are no more than 60 minutes/week in duration. Families of youth with ASD often have a variety of adjunctive services that they are reluctant to give up, and given the limited documentation of the efficacy of such interventions for social and emotional outcomes, it is deemed important to permit families to retain them in the service of recruiting a representative sample. If a potential participant is receiving non-allowed treatments at the time of the phone screen and wishes to discontinue them to enter the study, the patient will be asked to discuss this option with their clinician to determine safety and the child's best interest. In addition, we will obtain the patient's written consent to contact their clinician to determine the appropriateness of study participation. We will not influence the decision patients make with their clinician. If non-allowed psychosocial treatments are discontinued, the screening assessment will not be conducted until 1 month following termination.

(2) (a) Current clinically significant suicidality or (b) individuals who have engaged in suicidal behaviors within 6 months will be excluded and referred for appropriate clinical intervention.

(3) Child has been nonresponsive to an adequate trial of CBT for anxiety within the previous 2 years (at least 10 sessions over a period of less than 26 weeks conducted by a licensed provider of CBT). This will be determined through records review and speaking with the clinician if appropriate.

(4) Lifetime DSM-IV bipolar disorder, schizophrenia or schizoaffective disorder as assessed by all forms of information (i.e., clinical history, study measures, etc.).[80]

(5) Initiation of an antidepressant medication within 12 weeks before study enrollment or an antipsychotic medication 6 weeks before study enrollment or the child has changed the dose of an established medication within 8 weeks before study enrollment (4 weeks for antipsychotic) or during

psychotherapy (unless the dose is lowered because of side effects). If the child is on a medication, she or he can remain on it at its current dose. While in their arm, children will not be able to continue or initiate psychosocial interventions (psychotherapy, certain types of social skills training, applied behavior analysis targeting anxiety).

Initial Phone Screen. Individuals who meet basic eligibility requirements during the phone interview and remain interested will be invited for a screening visit, at which point a project staff will obtain informed consent from the parent.

Assessment Timeline. Participants will be randomized following screening to receive 16 weeks of BIACA, standard practice CBT, or to the 16-week TAU group. There is a 45% chance of being randomized to BIACA, 45% chance of being randomized to standard practice CBT, and 10% chance of being randomized to the TAU control (who will have their choice of interventions following the TAU phase). The Mid-treatment assessment will be done after session 8 or week 8 depending on condition. Within one week of the final treatment session or week 16, patients will complete the Post-treatment assessment. Youngsters randomized to a treatment condition will complete 6-month follow-ups. Consistent with other NIH-funded multimodal trials, families will be seen every four weeks for booster sessions during the Follow-up. Non-responders at Post-treatment will not be required to adhere to limited intervention services during the follow-up phase and will be provided with community treatment referrals (at cost to the family). If families deny the suggested maintenance plan for the follow-up phase (i.e. limited intervention services and monthly CBT sessions), a follow-up assessment will still be conducted. These families will be distinguished from those who adhere to the maintenance plan. If participants do not meet inclusion for the study, their baseline data will be kept and used in data analysis.

Treatment Conditions

Randomization. Participants will be randomized after screening to receive BIACA, standard care CBT or TAU. There is a 45% chance of being randomized to BIACA, 45% chance of being randomized to standard practice CBT, and 10% chance of being randomized to the TAU control. Randomization will not be revealed to IEs and variable block-lengths will be used within strata to maintain balance during enrollment while minimizing risks of unblinding. Postdoctoral clinical psychology fellows or advanced graduate trainees in clinical psychology will provide both CBT conditions to participants.

BIACA. Therapists will work with families for 16 weekly sessions, each lasting 90 minutes (45 minutes with the child and 45 minutes with the family/parents), implementing the Behavioral Interventions for Anxiety in Children with Autism (BIACA) manual.[81] The manual includes 4 anxiety coping skills training modules (e.g., affect recognition and cognitive restructuring), which are integrated into an acronym (the "KICK" plan) to help children remember the skills. Early in treatment, a comprehensive hierarchy is developed identifying all target behaviors, including anxious and avoidant behaviors, social skill deficits, restricted and repetitive behaviors, and behavioral problems. Ultimate goals are set forth as measureable outcomes (e.g., "engage in appropriate peer play 100% of the time during recess"), which permits the delineation of specific proximal goals that gradually increase in difficulty. Anxiety and all other target behaviors are addressed using in vivo exposure therapy techniques during sessions and in the community. Therapeutic concepts are taught using multimodal stimuli (e.g., discussion scaffolded by drawing, writing, photographs and cartoons, and acting) and guided Socratic questioning, relying upon children's special interests as metaphors to maintain enthusiasm and motivation. Children and parents are taught friendship skills (e.g., play-date hosting; joining peers at play) in several social modules. Parents (in weekly sessions) and school

personnel (in two 1-hour school consultations over the course of treatment) are taught to support children in entering and maintaining conversations or play. These skills are practiced at school, in the community, and on play-dates. During the school consultations, a peer "buddy" program is implemented to enhance social inclusion. Habit reversal procedures are implemented for repetitive behaviors, using incompatible replacement behaviors. All target behaviors are reinforced with a reward system. The BIACA program employs a modular format that is guided by a treatment algorithm[63] designed to address each child's unique clinical needs within the 16-session format.

Standard Practice CBT. Participants randomized to the Coping Cat program arm will receive 16 weekly 60-minute sessions that represent the standard practice CBT for anxiety that has been found to be effective in multiple trials.[35, 37, 38] The first eight sessions focus on teaching skills to the child, whereas the second eight sessions provide the child the opportunity to practice newly learned skills (through exposure tasks) both within and between sessions (homework). The goal is to teach youth to recognize the signs of unwanted anxious arousal and to let these signs serve as cues for the use of anxiety management strategies. The main features of this standard CBT are: (1) recognizing anxious feelings and somatic reactions to anxiety, (2) identifying cognition in anxiety-provoking situations (i.e., unrealistic or negative expectations), (3) developing a plan to cope with the situation (i.e. modifying anxious self-talk into coping self-talk as well as identifying coping actions that might be effective, (4) behavioral exposure tasks, and (5) evaluating performance and self-reinforcement for effort. The treatment uses behavioral training strategies such as modeling, imaginal and in-vivo exposure tasks, role-play, and contingent reinforcement. To help reinforce and generalize the skills, specific homework tasks are assigned. Parent involvement in the child's treatment occurs (weekly update, scheduling, etc.) and parents may be included in exposure tasks. Parents consult to the child's treatment, and given a model for assisting with the treatment in the role of the child's "cognitive behavioral coach." In addition to a regular 15-minute check-in at the start of each session, parents are scheduled for meetings with the therapist after the 3rd and 8th sessions, and prior to the end of treatment. Parents will be given a copy of the Parent Companion,[82] a pamphlet that describes their child's treatment and their potential contributions as parents to beneficial outcomes.

TAU Condition. Participants randomized to the TAU condition will wait for a period of 16 weeks before receiving treatment in the context of the study. During this time, youth may receive psychotherapy and/or initiate or change current psychiatric medication (if applicable). Eight weeks into the TAU period, youth will participate in a mid-point assessment. This assessment in conjunction with bi-weekly check-in calls will allow the research staff to monitor the participant during the TAU period. If a participant's anxiety worsens during this phase, the TAU period will be cut short and treatment will begin. After completion of the post assessment, these youth and their families will be offered treatment (BIACA or Coping Cat depending on their preference). The TAU control group will act as a comparison group for both forms of CBT (BIACA or Coping Cat). This control group allows us to examine potential differences in response due to standard care available in the community versus CBT especially in the instance that both CBT groups demonstrate good yet similar response rates. The risk of the TAU condition is necessary to provide feasibility data regarding the utility of CBT in treating youth with ASD and comorbid anxiety, as well as provide estimates of differential outcome. Although CBT is the gold standard for typically developing youth, this has not been sufficiently established in youth with ASD which is a gap in the literature that the current study aims to address. Past literature has examined standard CBT or CBT modified for ASD but none have compared the two.

Therapist Training. Experienced therapists, postdoctoral clinical psychology fellows or advanced graduate trainees in clinical psychology, under supervision, will provide treatment to participants (therapists will be

trained to provide either condition). Annual refresher training (and/or training new therapists) will be coordinated with a convention which therapists will be attending.

Treatment Integrity. Treatment integrity in both conditions will be monitored through the use of ongoing on-site and cross-site supervision, and regular monitoring and rating of audiotaped sessions. Treatment will follow the BIACA[81] or Coping Cat manuals developed in our past trials.[38] Adherence Checklists (for treatment integrity) have been developed in past NIH-funded work. [35, 38, 44] Integrity checks will assess the degree to which the treatment as described was indeed the treatment presented to participants. Across arms, 1-hour on-site clinical supervision will be held between sessions, and there will be weekly cross-site conference calls for all project therapists. All intervention sessions will be videotaped (with participant consent) and 30% of tapes will be randomly selected from each condition from each site for review and rating by the UCLA site under Drs. Wood's direction (for BIACA) and by the Temple site under Dr. Kendall's direction (for Coping Cat). Thus, therapists will not be aware of which sessions will be evaluated. Tapes will be rated by reliable raters using the adherence rating system to ensure the treatment protocols are being followed and that the treatments are distinct. We will also assess the degree to which each arm is distinct from the other treatment arm.

Assessments and Measures

Measures will be administered at Screening, Mid-treatment, Post-treatment, and 6-month Follow-up. Measures of anxiety were selected based on evidence of reliability and validity within the ASD population, and for evidence of divergence (negligible correlations) with measures of autism symptom severity.

Clinician Rated/Administered Measures

Anxiety Disorders Interview Schedule for DSM-IV: Parent Version (ADIS-IV-P).[83] The ADIS-IV P is a clinician-administered interview that assesses for the presence of *DSM-IV* disorders in children. It demonstrates reliability in anxiety assessment among youth with ASD[84] and will be administered to the parent at screening.

Autism Diagnostic Observation Schedule (ADOS-2).[75] The ADOS-2 is a structured observational assessment administered directly to the subject to elicit social interaction and use of language. The ADOS-2 will be administered at screening and post. Children must, at minimum, meet ASD criteria for the Social area to be eligible for the study.

Clinical Global Impression (CGI) Scales.[85] The CGI-Improvement is a 7-point rating of treatment response anchored by 1 ("very much improved") and 7 ("very much worse"). The CGI-Severity is a 7-point rating of severity anchored by 1 ("not at all ill") and 7 ("extremely ill").

The Childhood Autism Rating Scale- Second Edition (CARS-2HF)[86]. The CARS-2HF is a 15-item clinician administered diagnostic evaluation and direct observation measure of autism and autism severity. A clinician rates each item (i.e., relating to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste, smell and touch response and use, fear or nervousness, verbal communication, nonverbal communication, activity level, level and consistency of intellectual response, and general impressions) on a 4-point Likert scale ranging from 1= no evidence of difficulty, appropriate and normal, and 4 = severely abnormal. Psychometric support for the CARS in youth with autism includes good internal consistency, acceptable inter-rater reliability, test-retest stability,

discriminant validity and convergent validity.

Assessment of Fear Extinction (Fear Paradigm).[87] A novel experimental paradigm of fear conditioning/extinction paradigm will be computer-administered at the screening assessment. Three trials are collected over 30-minutes: pre-acquisition, acquisition, and extinction. During the pre-acquisition phase, children are presented with two neutral stimuli for 8 seconds each (i.e., pictures of two adult female faces). Following habituation, participants view these same two faces, but one face is paired with a moderately aversive stimulus (i.e., a brief 95 dB scream, the unconditioned stimulus [UCS]) over 8 trials while the other is not. This is followed by an extinction phase, consisting of 12 presentations of each female face without the UCS. Subjects indicate on a 10-point Likert scale the degree to which they feel afraid of the varied stimuli. Subjects are also connected to a small sensor on their palm that assesses skin conductance.

Feshbach Audiovisual Test for Empathy.[88] With the Feshbach, each child is presented with 5 two minute videos. The protagonist in each of these videos will be experiencing a different emotion (happiness, anger, pride, sadness, or fear). After each video, the child will be asked to identify what emotion the protagonist was feeling and to describe a time when the child has also felt that feeling.

Happe Strange Story Task. [89, 90] The Strange Story task is an advanced theory of mind task that assesses the participant's ability to interpret non-literal statements in a variety of stories. (For example: "When James sees Claire's huge dog, he says, 'Claire you haven't got a dog at all. You've got an elephant!'"). For each story, participants are asked to identify if the statement is true and then asked to identify a practical reason for the character's words or actions. Participants' responses are then rated on a 0–2 scale as fully correct, partially correct, or incorrect according to preset criteria. In previous trials, individuals with autism have performed less well on the task as compared to typically developing peers. [89-91]

We will be using a modified child version of the Iowa Gambling Task.[92] Garon and Moore (2004) adapted the original Iowa Gambling Task for children aged 6-13. Participants will be presented four sets of decks consisting of two "advantageous" decks and two "disadvantageous" decks. Two of the decks will have frequent losses (one advantageous and one disadvantageous deck), while the other two will have infrequent losses. However, instead of number symbols, animal pictures will be used to designate wins and losses. Each card from the disadvantageous decks will have two bear pictures, which indicate a win of two tokens, and some of the cards will have pictures of tigers, which indicate loss of tokens. Each card from the advantageous decks will have one bear picture, which indicates a win of one token, and some of the cards will have pictures of tigers, which indicate loss of tokens. A total of 80 cards will be used. Participants are told to accumulate as many tokens as possible by selecting cards and will receive prizes based on the total number of tokens they earn by the end of the task.

Pediatric Anxiety Rating Scale (PARS).[45] The PARS is a clinician-rated scale assessing anxiety symptoms and the associated severity and impairment in children over the past week. The Symptom Checklist consists of 59 items assessing 7 categories of anxiety symptoms. Scores on the PARS Severity Scale range from 0 to 25, with scores >14 consistent with clinically significant levels of anxiety in youth with and without ASD. The PARS has good reliability[45] and is sensitive to both pharmacologic and CBT treatment.[35]

Pediatric Accommodation Scale (PAS).[93] The PAS is a 16 item measure that assesses degree of reassurance needed, avoidance, parental involvement, and interference due to the child's anxiety over the past month.

Rage Outbursts and Anger Rating Scale (ROARS).[94] The ROARS is a 0 to 9 point scale measuring frequency, intensity, and duration of rage and anger. The participant does not have to do anything for this rating; the clinician rates it based on all available information.

Service Assessment for Children and Adolescents (SACA).[95] A modified version of the SACA will be used. The SACA is a psychometrically sound parent interview about the broad use of mental health services.

Wechsler Abbreviated Scale of Intelligence (WASI).[76] The WASI is a short (four subtests), individually administered test of intelligence for children and adults ages 6 through 89. The four-subtests (Vocabulary, Block Design, Matrix Reasoning, Similarities) can be administered in about 30 minutes. It has demonstrated acceptable to excellent psychometric properties and is the recommended instrument when a quick and accurate estimate of general intellectual functioning if needed.

Youth Top Problems (YTP).[96] The Youth Top Problems approach is a well-validated evidence based assessment procedure that is sensitive to treatment response and found to provide information separate from that generated by standard checklist ratings of child symptoms [96]. YTP scores have proven to be a valid measure of internalizing, externalizing, and total psychiatric symptoms among children involved in general mental health interventions when compared to much longer symptom checklists such as the CBCL and YSR, and are highly sensitive to treatment [96].To provide a clinical context for eliciting top problem reports from parents, a structured clinical interview pertaining to child psychiatric symptoms is administered to parents by a trained diagnostician. In this study, the diagnostic interview is the ADIS, to effectively focus parents' attention on anxiety symptoms. Then, parents are asked to state what problems that were just discussed are the most concerning to them. The diagnostician audiotapes this discussion and also writes the parents' responses down in their exact words.

Therapist Rated Measures:

Clinical Global Impression (CGI) Scales.[97] The CGI-Improvement is a 7-point rating of treatment response anchored by 1 ("very much improved") and 7 ("very much worse"). The CGI-Severity is a 7-point rating of severity anchored by 1 ("not at all ill") and 7 ("extremely ill").

Therapist Information Form (TIF).[98] The TIF is a 16-item therapist report form that assesses therapist demographics, training, practice experience, theoretical orientations and caseload associated with the study. This is completed at the first therapy session.

Youth Top Problems. The Youth Top Problems (YTP) [96 96 96 96 96 97 97] will be administered by the therapist at every session.

Parent-Rated Measures:

Autism Spectrum Rating Scales (ASRS).[99] The ASRS is used to identify symptoms, behaviors and features associated with Autism Spectrum Disorders. Parents use a five-point Likert rating scale to report how often they observe specific behaviors in the domains of Social/Communication, Unusual Behaviors and Self-Regulation.

Childhood Anxiety Impact Scale – Parent (CAIS-P).[100]
The CAIS-P is a parent report questionnaire of the impact of the child's anxiety on his/her psychosocial

functioning in certain situations.

Child Behavior Checklist (CBCL).[101] The CBCL is a 118-item parent-report measure of internalizing and externalizing problems with excellent psychometrics.

Children's Saving Inventory (CSI)[102] The CSI is a 23-item self-report measure designed to evaluate child hoarding behaviors. The CSI has demonstrated strong internal consistency (a=.84-.96), as well as strong convergent and discriminant validity.

Coping Questionnaire-Parent Version (CQ-P).[103] The CQ-P is 3-item parent-rated measure that assesses their child's coping (self-efficacy in anxiety provoking situations). Specifically, this measure asks parents to report on their child's top 3 most anxiety provoking situations.

Consumer Satisfaction Questionnaire (CSQ).[104] This measure consists of 14 items rating parents' level of satisfaction with the intervention their child received. Eleven of the items use a 7-point Likert response scale; the remaining 3 items are open-ended questions regarding the intervention.

Demographic Form**.** A brief demographics sheet, containing questions about marital status, family income, occupation, parental education, medical history, current medication and services etc. will provide information on a traditional set of predictors of treatment outcome.

Emotion Regulation Checklist (ERC; Shields & Cicchetti, 1997). The ERC is a 24-item other-report questionnaire that is scored on a 4-point Likert scale (1 = never; 2 = sometimes; 3 = often; 4 = almost always). It was designed to be completed by an adult who knows the child well, such as a parent (Shields & Cicchetti, 1998). The ERC assess parental perceptions of the child's emotion regulation and emotion lability.

Expectancy Rating Questionnaire (ERQ).[105] The ERQ will be given to parents at screening and after the adolescent's 4th therapy visit to assess treatment expectancy and credibility.

Family Accommodation Scale-Anxiety (FAS-A).[106] The FAS-A is a parent self-report that measures family accommodation in children with anxiety disorders. This nine item measure uses a 5-point Likert-type scale that assess how often accommodation occurs and displayed high internal consistency.

The HiPIC[107] includes 144 items grouped into 18 facets that are hierarchically organized under the higher order factors. Parents will be instructed to describe the child by the way he or she has most often behaved over the last year by indicating on a 5-point Likert-type scale the degree to which each statement was characteristic of the child to be assessed, with scale anchors labeled as barely characteristic, slightly characteristic, more or less characteristic, characteristic, and highly characteristic. The HiPIC's robust factor structure and high internal consistencies of domains and facets have been documented in various studies with clinical and nonclinical samples.[108-111] It will be used as a predictor of treatment outcomes.

MASC-P.[112] The MASC-P is a parent-report version of the MASC with excellent psychometric properties[113, 114] and treatment sensitivity in ASD populations.[115, 116].

Parent Expectancies for Therapy Scale (PETS).[117] The Parent expectancies for therapy scale (Kazdin & Holland, 1991) is a 25-item self-report measure that uses a 5-point scale to indicate the level of parent

expectancies (from low to high with 1= low and 5=high expectancy) for treatment in such domains as credibility of therapy, magnitude and rate of change likely to occur as a result of treatment, and the structure and amount of parental involvement that may be required by the treatment. This will be given at baseline assessment only.

Quality of Play Questionnaire: Parent (QPQ-P). [118] The QPQ-P is a parent-rated measure that assesses their child's play with peers during play dates. It contains 19 items that measure the child's type of play and interaction as well as the frequency of play dates.

Short Sensory Profile (SSP).[119] The SSP is a 38-item parent report form that assesses children's ability to process sensory information.

Social Responsiveness Scale (SRS-P).[120] The SRS-P is a 65-item scale measuring severity of autism spectrum symptoms (e.g., social awareness, autistic preoccupations) with excellent psychometrics.[44, 121]

Child-Report Measures:
Interviewers will read all items to the children (as children read along) to ensure understanding of item content.[115]

Abeer Children Dental Anxiety Scale (ACDAS).[122] The ACDAS is a measure of dental anxiety in children that employs a cognitive component. It is a 19 item scale that can be administered to children as young as 6. The ACDAS demonstrated excellent intra- and inter reliability, good concurrent validity, good discriminant validity and generalizability in the pilot trial.

Asher Loneliness Rating Scale (ALS).[123] The ALS is a self-report questionnaire that assesses children's perceptions of friendship quality and loneliness; this measure discriminates among children with autism and typically developing children [124] and have strong psychometrics.[18]

Big Five Questionnaire-Children (BFQ-C).[125] The BFQ-C is a 65-item questionnaire for children and adolescents developed by Barbaranelli and colleagues (2003). Children will be asked to complete this measure about themself using a Likert scale (1= Disagree strongly; 5= Agree strongly) based on how much they agree with statements made regarding their personalities. The items are written in accordance with the "Big Five"[126] personality factors of Openness (e.g. "I like to create new games and entertainments", "I would like very much to travel and to know the habits of other countries"), Conscientiousness (e.g. "Your child likes to keep all of his/her school things in order", "Your child plays only when he/she has finished his/her homework"), Extraversion (e.g. "I like to joke", "I easily makes friends"), Agreeableness (e.g. "If someone commits an injustice towards me, I forgive that person", "I trust others"), and Neuroticism (e.g. "I easily get angry", "I am sad"). It will serve as a predictor of treatment outcome.

Coping Questionnaire-Child Version (CQ-C). [103] The CQ-C is 3-item self-report measure that assesses coping (self-efficacy in anxiety provoking situations). Specifically, this measure asks children to report on the top 3 most anxiety provoking situations.

Negative Affectivity Self-Statement Questionnaire (NASSQ).[127] A modified version (33 items) of the NASSQ will be used in the study. This version contains the items that significantly separated youth with an anxiety disorder from youth that did not meet criteria for an anxiety disorder. The NASSQ is a child-rated measure that assesses anxious and depressed self-statements. The NASSQ has demonstrated acceptable

psychometric properties. [127, 128 129, 130]

Peer Victimization Scale (PVS).[131] The Peer Victimization Scale is a child self-report used to identify kids that are being bullied. Children who score higher on this measure indicate poor self-esteem and competence as well as greater depression. It has demonstrated concurrent validity as a measure of peer victimization.

Revised Children's Manifest Anxiety Scale: Second Edition (RCMAS-2).[132] The RCMAS-2 is a 49 item child self-report that measures different categories of anxiety (general, manifest or trait). The measure is presented in a yes/no format and consists of a Total Anxiety scale, three anxiety subscales and a Defensiveness scale. There is evidence supporting the construct validity of this measure and a test score stability coefficient of .64 to .76 was reported for a 1-week test-retest interval [133].

Satisfaction/Expectancy Measures.

Therapeutic Alliance Scale for Children-Revised (TASC-R).[134] The TASC-R is a 4-point Likert-type child-; parent-; and therapist- reported questionnaire that has 12 items measuring child-therapist and parent-therapist therapeutic alliances during treatment. The 12 items are written statements. For example, a written statement for a child would be "I like spending time with my therapist" and would have four choices to circle with 1 = not like you; 2 = a little like you; 3 = mostly like you; and 4 = very much like you. The TASC-R measures two constructs of affect towards therapy: bond and negativity. Cronbach's alpha internal consistency for bond and negativity are .72 and .74 respectively. The TASC-R has been used to show that child-therapist alliance predicts therapeutic change in both therapist and child measures of child improvements (Kazdin, Marcian, & Whitley, 2005).

Expectancy Rating Questionnaire (ERQ).[105] The ERQ will be given to parents at screening and after the child's fourth therapy visit to assess treatment expectancy and credibility.

Treatment Adherence and Differentiation Measures.

CBT Checklist (CBTC).[135] This 24-item measure evaluates therapist treatment integrity. More specifically, the CBTC assesses manual adherence, treatment implementation, and overall skill in CBT. The supervisor will complete this form on a weekly basis.

Supervisor Rating Form (SRF).[136] The SRF is a 30-item measure completed by the CBT supervisor that assesses the supervisor's global impression of the therapist's CBT competence and in-session style. The supervisor will complete this form following the therapist's last session with his or her final study participant.

Maintaining IE Blind. Clinicians and participants cannot be blinded to treatment assignment. Accordingly, IEs will be employed to provide unbiased information on the differential efficacy of treatments. Children and their families will be provided with both written and verbal reminders prior to each assessment, emphasizing that they not disclose treatment-identifying information to the IE. IEs will not attend clinical supervision meetings, will have an office location separate from where clinical services are provided, and will be trained to avoid any discussion of treatment programs with families. They will have no contact with families other than the assessments. However, because all youth are receiving treatment, seeing the child in clinic will not unblind the IE.

Analytic Design

Numerical and graphical descriptive statistics will be used to summarize the data on all randomized patients and to confirm the absence of group or site differences in screening demographic and clinical characteristics. Distributional assumptions will be checked and appropriate transformations or non-parametric methods will be applied as necessary. Our primary hypotheses concern differential change over time in anxiety symptoms and CGI-I scores for the treatment conditions. To maximize the efficiency of parameter estimates and to enable us to detect the most detailed possible patterns of treatment effects, we will analyze the outcomes using treatment arms simultaneously, employing general linear mixed models (GLMMs)[137] with group (BIACA, Coping Cat) and time as main effects, and a group x time interaction. The primary hypotheses will then be evaluated with the group x time interaction term. Our analyses will employ identity and logistic links respectively for continuous and binary outcomes with an unstructured covariance structure to allow maximum flexibility for the relationships within and between groups. Mixed models automatically handle missing data, producing unbiased parameter estimates via maximum likelihood techniques as long as observations are missing at random.[138, 139] This will allow us to use all available data from all subjects in an intention-to-treat (ITT) framework. Moreover, we are able to adjust for the presence of multiple recruitment sites by including this characteristic as a nested variable in the model. We are also able to control for potential confounding variables in terms of their impact on group differences and changes over time. To protect against Type I error, the principal analyses are designed to answer clearly stated major research hypotheses and are based on well-specified dependent variables. All tests will be reported using two-tailed family-wise significance level α=.05, using the Holm-Bonferroni correction.[140]

Definition of Primary Outcome Measures: The PARS and CGI-I are the primary outcomes. Consistent with CAMS,[35] we define treatment response as a CGI-I rating of 5 or 6 (much/very much improved).

Specific Analyses for the Individual Study Aims: Aims 1-2: For Primary Aim 1, to model anxiety symptoms, we will use the PARS as the dependent measure in a mixed effects regression with condition as the between-subject factor, time (Screening, Mid-treatment, Post-Treatment) as the within-subject factor and a Condition x Time interaction, with the latter used as evidence for differential rates of change. For the dichotomous outcome, treatment response (Aim 2), we will also use mixed effects regression, this time with a logistic link, with treatment condition, time (here Mid-treatment and Post-Treatment), and a Condition x Time interaction. Our primary interest is in the contrast at the end of acute treatment. The relevant continuous assessment measures for Aim 2 are described in detail in section C.5. (e.g., POPE, SRS); these scales will be assessed with the same model as in Aim 1. Aim 3: For continuous outcomes, the models of Aims 1-2 will be refit for responders only, adding the 6-month follow-up time point. Within-subjects contrasts between the follow-up time point and screening will allow us to test whether and when subjects remain significantly improved post-treatment. Evidence of deterioration (e.g., increased symptoms) over the follow-up period will also be of interest. Since all subjects in this analysis are by definition responders at treatment conclusion, we will use mixed effects logistic regression to model the likelihood of relapse or recurrence over the follow-up period. We will also report the proportions of subjects within each treatment arm who ever relapse or experience recurrence. Aim 4: To examine moderation, the interaction term between treatment condition and ASD severity will be used to examine changes over time for the continuous (PARS scores) and categorical outcomes (responder status; CGI-I). Significant interactions will be followed up by stratifying on treatment condition and examining parameter estimates, with 95% CI, for ASD severity and the outcomes. Exploratory Aim 5: Testing the mediation hypothesis requires that the direct path is meaningfully attenuated when the mediator is in the model and is also a significant predictor

of outcome. Significant effects yielded in tests of Aims 1-2 will be further evaluated by including the mid-treatment mediator variables specified in B.2 in separate linear regression models and will employ bootstrapped estimates of the indirect effects.[141] Aim 6: The same analytic plan for tests of moderation will be applied with select potential moderators.

Power Analyses and Sample Size Considerations: We will aim to enroll a total of N=201 subjects, randomizing 90 to each treatment arm and 21 to the TAU arm. This sample size was chosen to provide the optimal balance between feasibility of recruitment and maximization of power for the primary and secondary aims outlined above. Assuming an attrition rate of 10% over the acute treatment period and another 15% over the 6 month follow-up, which is conservative based on our prior experience,[35, 44, 46] we expect to have approximately 81 participants per treatment condition at the end of acute treatment and 57 per treatment condition at the end of follow-up. All calculations use a 2-sided significance level of α=.05 and assume a moderate correlation of r=.5 between time points within subjects, consistent with our previous CBT study.[44] Under these assumptions, using GLMM for continuous outcomes we have at least 80% power to detect a constant two-group (BIACA treatment vs Coping Cat program) difference of d=.47 averaged over the two post-screening treatment time points (Mid- and Post-treatment) for Aims 1-3. There is at least 80% power to detect the condition x time interaction represented by a change from no difference at Screening to a difference of d=.33 at Post-treatment. These power calculations are conservative in that they are based on evaluating the two active treatment effects independently (i.e., in separate models). Our actual power, using a single two-arm model, will be higher as simultaneous estimation of the contrasts leads to smaller standard errors. Data from a pilot trial comparing BIACA to a waitlist group yielded a very large effect size of d=2.5 on the ADIS-CSR anxiety severity scale at Post-treatment and a medium to large effect size of d=.75 on the SRS (measure of autism symptoms).[22, 44] Although one might suspect the group differences to narrow with larger sample sizes and an active therapy comparison, our power should clearly be adequate to detect the treatment effects of primary interest. Further, our power is sufficient to detect group differences at any one time point, with group differences in the order of d = .44 during the acute treatment period and d = .53 at the 6 month follow-up resulting in 80% power at alpha = .05. For treatment response, simulations for a two conditions (two treatments) logistic mixed model, starting with 81 subjects per condition and assuming reasonable differential response rate, showed over 80% power to detect a treatment effect. The two-sample test of proportions, which corresponds most specifically to the primary hypothesis, can detect a response rate difference of 30% between the treatment conditions at the end of acute treatment with over 90% power using ITT LOCF (n=57 per group). Our pilot data for BIACA show response rates of 75-79%[44, 46] in the BIACA versus 8.7-14% for waitlist and usual care groups, respectively. We expect a higher response rate using the standard care comparison. However, even under the very conservative assumption that the response rate in our comparison arm is over four times as high as what was observed in our pilot studies,[44, 46] our design has excellent power. For moderator analyses, 80% will be achieved for interaction terms that account for at least 6% of variance. As a result, we have identified ASD severity as the most salient and relevant potential moderator of treatment outcomes. Calculations for the continuous outcome mixed models were performed in Hedeker's RMASS2 software and calculations for the logistic mixed models were done via simulation in the R statistical package.

Missing Data and Attrition: Our primary analytic tool is GLMM, which provides unbiased parameter estimates when data are missing at random. GLMM estimates are based on maximum likelihood techniques and do not require imputation. Because the intermediate time points for subjects who do not complete the full protocol provide information about their trajectory, we feel this is more appropriate than LOCF, which assumes a flat trajectory. However, we recognize that if dropout that is differentially

associated with outcomes in a way not captured by the available trajectories (i.e., non-ignorable rather than MCAR/MAR), this could compromise treatment comparisons. We will attempt to identify possible sampling biases by performing multiple logistic regression analyses on dropout using measures of clinical status at screening or prior to dropout as covariates. If warranted, we will use imputation and propensity score approaches to handle bias problems. Every effort will be made to prevent dropouts/missing data, or to complete relevant assessments for patients who drop out.

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