Description of Study (v5.0)

Title: Specifying and Treating the Anxiety Phenotype in Autism Spectrum Disorder

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Purpose, aims, and objectives

Approximately 40%-80% of children and adolescents with autism spectrum disorder (ASD) exhibit clinically significant anxiety symptoms [1-4]. These symptoms are associated with increased social deficits, depression, irritability, and stereotyped and self-injurious behaviors [3, 5, 6]. Children and adolescents with anxiety also frequently avoid potentially stressful situations, thereby missing opportunities to learn important new skills [7]. Despite the significant consequences of anxiety symptoms, several critical treatment-relevant issues remain unresolved. First, there is a lack of clarity about how to differentiate ASD and anxiety symptoms. Second, little is known about how anxiety manifests in those with ASD and intellectual disability (ID). Third, the neural substrates of anxiety in ASD are poorly understood. The overarching goal of this project is to investigate these open issues in order to make interventions more precise, more personalized, and more likely to promote positive outcomes -- an objective consistent with the NIH the Roadmap, Precision Medicine, and Research Domain Criteria Project (RDoC) Initiatives and the IACC Strategic Plan, Chapter 4.

While there is no doubt that anxiety is a very serious issue for those with ASD, what to do about this problem is less clear. The search for empirically-validated treatments has begun with multiple small trials providing promising evidence that selective serotonin reuptake inhibitors (SSRIs) [8] and cognitive behavior therapy (CBT) [9]might reduce anxiety in those with ASD. However, this work is in its early stages. There is a great need for large, rigorously designed trials that validate the effectiveness of both medication and CBT, as well as functional neuroimaging studies that identify neural predictors of treatment efficacy and markers of therapy-induced change. Such work holds the potential to help answer the questions posed above and to assist the field in developing more personalized treatments. In Project 1 of the Center for the Development of Phenotype-Based Treatments of Autism Spectrum Disorder, we leverage the large, well-characterized UC Davis MIND Institute Autism Phenome Project (APP) cohort to conduct a comparative efficacy trial in N=132 participants (ages 8-12 years) with ASD and clinically significant anxiety. We take a precision medicine perspective and carefully examine youth with ID in a study with the following Specific Aims:

Specific Aim 1: To better characterize the sub-group of children and preadolescents with ASD that exhibit clinically significant anxiety. We use clinician-administered gold standard assays of traditional DSM (Pediatric Anxiety Rating Scale [PARS] and the Anxiety Disorders Interview Schedule-IV [ADIS-IV]), and nontraditional ASD-related anxiety symptoms (Autism Spectrum Addendum to the ADIS [ASDD]), as well as parent reports of potentially overlapping symptoms that complicate the ASD anxiety phenotype.

Specific Aim 2: To conduct a 16-week randomized comparative treatment trial of Behavioral Intervention for Anxiety in Children with Autism (BIACA) [10-12], sertraline, and placebo in youth with ASD, IQ>50, and clinically significant anxiety as assessed by a PARS score that is greater than or equal to 8.

Specific Aim 3: To use fMRI to investigate neural predictors of treatment efficacy, markers of treatment induced change, and signatures of anxiety sub-types from Aim 1.

Recruitment, Screening, and Inclusion/Exclusion Criteria

The Recruitment and Retention Core (RRC) of the UC Davis MIND Institute Center for the Development of Phenotype-Based Treatments of Autism Spectrum Disorder will provide a centralized resource for initiating and maintaining contact with participants involved in all Projects of the Center, which includes this study. The RRC will

serve as a liaison between Project Leaders and participants and their families to ensure that both project and family needs are being met. The study will utilize the RCC to identify and recruit eligible participants.

We will utilize a two part screening procedure to recruit eligible participants. The RCC will assist in identifying children who meet basic eligibility criteria (ASD diagnosis [formal or suspected by medical/psychology professional], 8-14 years of age) for Gate A (initial phone screen). Gate B will involve pre-testing with Project 1 clinicians to determine specific study eligibility based on a confirmation of ASD diagnosis, IQ and anxiety measures. It is anticipated that approximately 50% of the children who undergo Gate B screening will meet criteria for a clinically significant anxiety disorder and qualify for the study. The RCC will ensure that a sufficient number of participants are available for Gate A screening in order to obtain a total sample size of 132 children.

In addition we will recruit up to an additional 40 participants under a training Informed Consent Form (ICF) to ensure study staff and clinicians are proficient in administering the study assessments in preparation for beginning the clinical trial phase of the study. The training group participants will be between the ages of 6 and 17 and either typically developing, have an intellectual disability, or an ASD diagnosis.

Inclusion Criteria (Clinical Trial Phase only):

1) Outpatient boys and girls with ASD between ages 8-14 years at time of consent
2) Meets criteria for a diagnosis of ASD in one of the following ways:
    a. An ADOS assessment performed as part of the study with a score indicative of a diagnosis of ASD
    b. A diagnosis of ASD from a community or research provider or school district that uses gold standard measures (ADOS/ADI-R/SCQ) completed within the last 3 years, a score of 15 or greater on the SCQ, and meeting for ASD on the DSM-V Checklist
    c. An ADI-R score indicative of ASD, meeting for ASD on the DSM-V Checklist, and a BOSA or CARS score suggestive of a diagnosis of ASD
3) Meets criteria for clinically significant anxiety symptoms as defined by a minimum score of 8 on the PARS Severity Scale (using the 5-item scoring method)
4) Meets criteria for clinically significant anxiety symptoms as defined by qualifying for diagnosis on 1 or more non-phobia items on the ADIS
5) The child has a Verbal Comprehension IQ greater than 50 as assessed on the Wechsler Abbreviated Scales of Intelligence or other standardized cognitive measure (e.g., WISC, Stanford Binet, DAS-II School Age)
6) Anxiety symptoms are considered the primary mental health problem (i.e., most impairing/distressing)
    a. For subjects presenting with comorbid symptomology (e.g., depression, tic disorder, or disruptive behavior disorders), eligibility will be guided by the following principle: the co-morbid conditions cannot be sufficiently severe to:
        i. warrant immediate treatment or require a change in an otherwise stable psychosocial treatment regimen for that disorder, or
        ii. potentially interfere with the child's ability to comply with the study assessment and treatment batteries.
7) Stable medication regimen for 8 weeks prior to screening visit, including alternative medication, nutritionals, or therapeutic diets.
    a. The use of stable stimulant medications will be allowed if the dose has been consistent and the family and/or treating physician affirm there is no plan to alter the dose or change medication in the foreseeable future.
    b. If a potential participant is taking non-allowed psychotropic medication (antidepressants, antipsychotics) at the time of the phone evaluation and wishes to discontinue this medication to enter the study, the patient's parent will be asked to discuss this option with their prescribing physician to determine whether medication discontinuation would be safe and in the child's best interest. If a study physician has concerns the potential participant may be asked to provide documentation confirming the appropriateness of study participation. We will not influence the decision patients make with their prescribing physician.
8) Stable non-psychotherapy regimen for 4 weeks prior to screening visits. Non-psychotherapy regimen may include:

a. Academic tutoring
b. Occupational therapy
c. Speech therapy
d. School aides

9) Stable psychosocial treatment regimen for 4 weeks prior to screening visits. Allowed psychosocial treatments may include:
    a. School counseling (no more than 60 minutes per week in duration)
    b. Psychotherapy
    c. Social skills training
    d. Applied behavior analysis (ABA) (up to 10 hours per week)

Exclusion Criteria (Clinical Trial Phase only):

1) Subject is receiving significant concurrent psychosocial treatment with the primary aim to treat the child's anxiety.
    a. Families will have the option of discontinuing such services to enroll in the study. If a potential participant is receiving non-allowed treatments at the time of the phone evaluation and wishes to discontinue these treatments to enter the study, the patient will be asked to discuss this option with their clinician to determine whether termination would be safe and in the child‘s best interest. We will not influence the decision patients make with their clinician.
2) History of intolerance to sertraline OR previous unsuccessful treatment with sertraline or other SSRIs judged adequate in dose (per list below) and taken for at least 6 weeks, within the past 12 months.
    a. Sertraline - 100mg/daily
    b. Citalopram or paroxetine - 30mg/daily
    c. Escitalopram - 20mg/daily
    d. Fluoxetine - 20mg/daily
    e. Fluvoxamine - 100mg/daily
3) Current clinically significant suicidal behaviors with intent or plan or individuals who have engaged in suicidal behaviors within 6 months. Study physicians will direct patient to appropriate clinical care if these behaviors are seen.
4) Child has unsuccessful treatment for anxiety using a manualized CBT program within the previous 2 years (at least 10 sessions over a period of less than 1 year conducted by a licensed provider of CBT). This will be determined through parent report, records review and speaking with the clinician if appropriate.
5) Lifetime DSM-5 bipolar disorder, schizophrenia or schizoaffective disorder as assessed by all forms of information (i.e., clinical history, data from the ADIS-IV, etc.).
6) Abnormal laboratory or electrocardiogram results at screening that are in the opinion of the investigator clinically significant and may jeopardize the safety of the study subject.
7) Child has a major neurological disorder or medical illness that requires a prohibited episodic or chronic systemic medication that might interfere with the absorption, distribution, metabolism, or excretion of the study medication, or places the subject at increased risk, or that would interfere with study participation (e.g., frequent hospitalizations, frequent school absences).
8) Child pregnancy as indicated by history or positive pregnancy test.
9) Inability to safely swallow study medication after pill swallowing education.
10) Child and parent/caregiver who do not speak English.

Recruitment

A total of up to 172 participants will be recruited for this project. Project 1, the clinical trial phase, will recruit 132 participants, and up to an additional 40 participants will be recruited under a training consent to ensure study clinicians are proficient on administering the study assessments in the study population.

A subset of participants (anticipated n = 41) will be recruited from the ongoing Autism Phenome Project. The APP consists of 189 participants with ASD, who consented to be part of the longitudinal study. The APP is currently funded [1R01MH103284 (PI: Solomon) and 1R01MH103371 (PI: Amaral); IRB: 220915] to conduct longitudinal

cognitive and MRI assessments of children in the cohort between 8-12 years of age. It is anticipated that a subset of participants from these ongoing studies will meet inclusion criteria for the studies proposed on Project 1. For recruitment from the APP, participants will be informed about Project 1 studies either during their ongoing APP visits or contacted by the Recruitment and Retention Core RRC personnel.

In order to meet the targeted sample size of 132 for Project 1, other recruitment strategies will also be implemented. Participants will be recruited from the following sources:

a) The MIND Institute Childhood Autism Risks from Genetics and the Environment (CHARGE) Study, a large ongoing study with 100 children in the eligible age range of 8-14(PI: Hertz-Picciotto)
b) The MIND Institute Anxiety Clinic, headed by Dr. Breanna Winder-Patel, which has been at full capacity since December 2014, receives an average of 6 new referrals per month and maintains a waitlist of 8-12 months. Children who meet eligibility criteria will be informed about Project 1
c) Dr. Jeff Wood at UCLA will inform the UCLA autism clinics and providers and local autism contacts in the Southern California area of Project 1
d) The MIND Institute Research Volunteer Registry, RVR (in conjunction with the IDDRC CT Core), which currently has 348 children with ASD in the 8-12-years-old age range, and d) from the greater Sacramento community (which includes the Bay Area - San Francisco, Oakland, San Jose etc. and central valley cities such as Modesto, Stockton and Merced) through community outreach events (in conjunction with the IDDRC CT Core).
e) The cohort discovery tool based on the Electronic Medical Records (EMR) and MyChart systems through UC Davis Health will also be utilized to query the systems and identify prospective subjects for recruitment by following the process for EMR data retrieval and recruitment.
f) Referrals from community providers and other UCD Health physicians/clinics
g) Testimonials from previous study participants/families to help potential participant families better understand what participation in the study entails. We will ask interested participant families to provide a brief description of their personal experience, done in writing or via video. These statements will be available for viewing via the study's website, MIND Institute websites, and/or the MIND Institute YouTube page. These statements will include a note that they represent the opinions and personal experience of the families, and direct families interested in more specific information to contact the study team with questions. In collecting and using these materials, the study will follow UC Davis Health policy 1426 for appropriate authorization and consent.

Participants will be recruited using a short recruitment statement which may be mailed, emailed , or posted on list serves or social media associated with ASD or neurodevelopmental disorders or through community organizations. Potential participants may also be recruited through a study specific webpage listed under the UC Davis MIND Institute website. Recruitment flyers, brochures, and posters may be placed around UCDHS facilities or distributed at recruitment events or other locations with appropriate recruitment populations. Press releases or presentations/talks by study staff related to autism or anxiety may also be used as recruitment tools.

Joint advertising materials may be used in conjunction with other studies at the MIND Institute which have overlapping eligibility criteria. Joint materials may also be used to advertise the Autism Center of Excellence as a whole, including the Center's research studies—the BRAIN and SC2BC studies (IRB #1097084)—and/or the Center's related programs (e.g., community outreach or education opportunities).

The research procedures for recruitment purposes require accessing personal health information (PHI) to identify prospective subjects without HIPAA Authorization. The research team will identify potential subjects and access medical records to help verify eligibility prior to the treating physician and/or research coordinator approaching the potential subject. The review of a potential subject's medical records is for limited information and only to determine eligibility. The data are derived from clinically indicated procedures and there is minimal risk to the potential subject's status, employment, or insurability. Only research personnel will access medical records via the Electronic Medical Record system (EMR), and all personnel are required to use the "Quick Disclosure" function in EMR to document viewing the individual's record. Consent to participate and HIPAA Authorization to access additional information in the medical records will be obtained at the time of enrollment into the study.

Timelines

This project will consist of two phases. Phase 1 will place participants into either CBT treatment, or sertraline or placebo groups. These subjects will follow a schedule of treatment and check-ins with the study team as follows:

Gate A: Preliminary Screening				
Visit	***Week***			
1	0	**Gate B: Consent & Assessments** *(Assessments may be split into multiple days to accommodate family schedule; all components to be completed within 60 days of consent date)* Qualification & pre-treatment assessments Randomization		
		Phase 1: Treatment		
		If randomized to CBT Arm:	***If randomized to Med Arm (sertraline or placebo):***	
		Visit Schedule	*Visit Schedule*	*Dispensation Schedule**
				12.5mg/day (2wk supply)
2	1	BIACA therapy (Office/Remote)	Office/Remote visit	*No planned dispensation; subject to continue taking medication at current dose daily*
3	2	BIACA therapy (Office/Remote)	Office/Remote visit	25mg/day (2wk supply)
4	3	BIACA therapy (Office/Remote)	Office/Remote visit	*No planned dispensation; subject to continue taking medication at current dose daily*
5	4	BIACA therapy (Office/Remote)	Office/Remote visit	37.5mg/day (2wk supply)
6	5	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
7	6	BIACA therapy (Office/Remote)	Office/Remote visit	50mg/day (2wk supply)
8	7	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
9	8	BIACA therapy (Office/Remote)	Office visit	62.5mg/day (2wk supply)
10	9	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
11	10	BIACA therapy (Office/Remote)	Office/Remote visit	75mg/day (2wk supply)
12	11	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
13	12	BIACA therapy (Office/Remote)	Office/Remote visit	100mg/day (2wk supply)
14	13	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
15	14	BIACA therapy (Office/Remote)	Office/Remote visit	125mg/day (2wk supply)

16	15	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
17	16	BIACA therapy (Office/Remote)	Office/Remote Visit	Down-titration begins, per additional table below
		Phase 1: Post-treatment assessments *(Assessments may be split into multiple days to accommodate family schedule; all components to be completed within 2 weeks of last treatment visit)*		
	17	Up to 3 BIACA booster sessions (Office/Remote)	Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
	18		Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
	19		Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
	20		Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
18	21-22	Office/Remote Visit: To be completed between weeks 21 and 22		
19	28	Phone Call: 3-month follow-up assessment (the placebo group will then be offered to participate in Phase 2 with treatment starting within 60 days from visit 19)		

** Or minimum effective dose using the rationale below. Study physicians may choose to stop or slow down titration depending on subject tolerance.*

If a subject has completed an ADOS and/or WASI or other comparable IQ measure (WISC, Stanford Binet, DAS-II School Age) within 2 years prior to STAAR enrollment through participation in another MIND Institute research study or through a community provider, using a reliable assessor, the family will be given the option to provide consent for copies of the assessment(s) to the STAAR study instead of repeating these measures during the Gate B assessment phase of the study.

We will be following the model of the CAMS Trial (NIMH Child Anxiety Multimodal Treatment Study) which compared sertraline, CBT, and their combination to placebo in 488 typically developing youth aged 7-17 with a primary anxiety disorder. We will be using a "fixed-flexible" schedule, similar to the CAMS Trial.

Subjects randomized into the therapy group will participate in weekly BIACA therapy sessions according to the table above. The clinician will also administer the PARS and CGI-I at 6 timepoints to measure responsiveness to treatment. Possible adverse events and concomitant medications will also be assessed and reviewed by a study physician if needed.

All subjects in the medication or placebo groups (regardless of age/weight) will begin Phase 1 of the trial at the 12.5mg/d dose. Dose increases will be made according to the table above, every other week for the next 14 weeks unless there is concern about the emergence of potential side effects that would justify deferring a dosage increase or that the patient already has achieved a therapeutic dose based on the study physician's evaluation. In the event of the emergence of adverse events during treatment (including between scheduled visits), the study physician may elect to revert to the next lower medication dose in the titration table (either 12.5 or 25mg increments depending on current dose and doctor's clinical judgement). Sertraline or placebo will be given orally once daily in capsule form. Timing of drug administration may be adapted as necessary for tolerability. Thus, some children may get the drug as a single dose in the morning or at bedtime; others may require that the dose be divided to achieve better tolerability.

Sertraline tablets will be over-encapsulated by the Investigational Drug Services (IDS) pharmacy to enable matching placebo capsules to be produced and maintain the blind among study staff and study subjects. Randomization will be computer-generated and will stratify on Verbal Comprehension IQ (≥70 vs. <70) and age

(≥11yrs vs. <11yrs) (standardization sample median as the cutoff) to maximize power for moderator tests. Drug accountability for the medication groups will be conducted by study staff at all office/remote visits 2 through 18. If compliance falls below 80% the participant and caregiver will be re-trained on study dosing and will be discontinued from study if the compliance requirement is not met at subsequent visits.

At visit 17 (week 16) all subjects will complete the post-treatment assessments. These assessments will be done within a two week window, including the behavioral, cognitive testing, and neuroimaging. Based on the respective study group, subjects will discontinue either the therapy or begin the down titration for the study medication. Those in the medication group will discontinue the study medication over a 5 week period according to the titration schedule in the above table. Dose decreases will be no greater than 50mg/daily for each of the 5 weeks and weekly phone calls will be conducted with the subject and a study physician to monitor the medication down titration. Appropriate action will be taken by study staff if significant issues or behavioral concerns arise for a subject. At the end of the 5 week down-titration period the sertraline and placebo groups will return for a visit 18 between weeks 21 and 22 to return the study medication and to conduct a brief safety review. Those in the therapy group will be given up to 3 booster sessions during this 5-week time period. These sessions will serve as a wind-down from the therapy program and are designed to reduce sudden recurrence of anxiety symptoms due to an abrupt end of therapy.

At the end of week 28, the three month follow-up visit 19 phone call will be conducted with all subjects and/or parents, to collect additional behavioral assessments as well as follow-up on any unresolved adverse events if necessary. After the Phase 1 follow-up assessments are completed, the study team will be unblinded to the treatment arm for subjects in the medication group and those in the placebo group will be offered the option of participating in phase 2 of the study where subjects will receive their treatment of choice (sertraline or CBT).

Phase 2 of the study will provide subjects randomized into the placebo group during Phase 1 access to the study treatment of their choice in order to maintain equitable treatment among study subjects. The subjects who wish to continue in Phase 2 will need to begin treatment within 60 days of completing the 3 month follow-up visit 19. These subjects will follow a schedule of treatment and check-ins with the study team as follows:

<table>
<tr><th colspan="5">Phase 2: Treatment</th></tr>
<tr><td><u>Visit</u></td><td><u>Week</u></td><td colspan="3"></td></tr>
<tr><td rowspan="4">1</td><td rowspan="4">0</td><td colspan="3">Phase 1: Follow-up Visit 19
(Assessments from Phase 1 follow-up visit 19 will serve as Phase 2 baseline assessments)
Pre-treatment assessments & Randomization</td></tr>
<tr><td>If randomized to CBT Arm:</td><td colspan="2">If randomized to Med Arm (sertraline):</td></tr>
<tr><td><u>Visit Schedule</u></td><td><u>Visit Schedule</u></td><td><u>Dispensation Schedule*</u></td></tr>
<tr><td></td><td></td><td>12.5mg/day (2wk supply)</td></tr>
<tr><td>2</td><td>1</td><td>BIACA therapy (Office/Remote)</td><td>Office/Remote visit</td><td>No planned dispensation; subject to continue taking medication at current dose daily</td></tr>
<tr><td>3</td><td>2</td><td>BIACA therapy (Office/Remote)</td><td>Office/Remote visit</td><td>25mg/day (2wk supply)</td></tr>
<tr><td>4</td><td>3</td><td>BIACA therapy (Office/Remote)</td><td>Office/Remote visit</td><td>No planned dispensation; subject to continue taking medication at current dose daily</td></tr>
<tr><td>5</td><td>4</td><td>BIACA therapy (Office/Remote)</td><td>Office/Remote visit</td><td>50mg/day (2wk supply)</td></tr>
<tr><td>6</td><td>5</td><td>BIACA therapy (Office/Remote)</td><td>Phone Call</td><td>No planned dispensation; subject to continue taking medication at current dose daily</td></tr>
<tr><td>7</td><td>6</td><td>BIACA therapy (Office/Remote)</td><td>Office visit</td><td>75mg/day (2wk supply)</td></tr>
</table>

8	7	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
9	8	BIACA therapy (Office/Remote)	Office/Remote visit	100mg/day(2wk supply)
10	9	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
11	10	BIACA therapy (Office/Remote)	Office/Remote visit	125mg/day (2wk supply)
12	11	BIACA therapy (Office/Remote)	Phone Call	*No planned dispensation; subject to continue taking medication at current dose daily*
13	12	BIACA therapy (Office/Remote)	Office/Remote Visit	Down-titration begins, per additional table below
		Phase 2: Post-treatment assessments *(Assessments may be split into multiple days to accommodate family schedule; all components to be completed within 2 weeks of last treatment visit)*		
	13	Up to 3 BIACA booster sessions (Office/Remote)	Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
	14		Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
	15		Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
	16		Phone Call	Continue down-titration (decrease by no more than 50mg/day increments)
14	17-18	Office/Remote Visit: To be completed between weeks 17 and 18		
15	24	Phone Call: 3-month follow-up assessment		

* Or minimum effective dose using the rationale below. Study physicians may choose to stop or slow down titration depending on subject tolerance.

Subjects randomized into the therapy group will participate in weekly BIACA therapy sessions according to the table above. The clinician will also administer the PARS and CGI-I at 5 timepoints to measure responsiveness to treatment. Possible adverse events and concomitant medications will also be assessed and reviewed by a study physician if needed.

All subjects in the Phase 2 medication group (regardless of age/weight) will begin at the 12.5mg/d dose. Dose increases will be made according to the table above, every other week for the next 10 weeks unless there is concern about the emergence of potential side effects that would justify deferring a dosage increase or that the patient already has achieved a therapeutic dose based on the study physician's evaluation. In the event of the emergence of adverse events during treatment (including between scheduled visits), the study physician may elect to revert to the next lower medication dose in the titration table (either 12.5 or 25mg increments depending on current dose and doctor's clinical judgement). Sertraline will be given orally once daily in capsule form. Timing of drug administration may be adapted as necessary for tolerability. Thus, some children may get the drug as a single dose in the morning or at bedtime; others may require that the dose be divided to achieve better tolerability.

The Phase 2 Sertraline study medication will be managed by the Investigational Drug Services (IDS) pharmacy to ensure proper dispensation and destruction. Drug accountability for the medication group will be conducted by study staff at all office/remote visits 2 through 14. If compliance falls below 80% the participant and caregiver will be re-trained on study dosing and will be discontinued from study if the compliance requirement is not met at subsequent visits.

At Phase 2 visit 13 (week 12) subjects will complete the post-treatment assessments. These assessments will be done within a two week window. Based on the respective study group, subjects will discontinue either the therapy or begin the down titration for the study medication. Those in the medication group will discontinue the study medication over a 5 week period according to the titration schedule in the above table. Dose decreases will be no greater than 50mg/daily for each of the 5 weeks and weekly phone calls will be conducted with the subject and a study physician to monitor the medication down titration. Appropriate action will be taken by study staff if significant issues or behavioral concerns arise for a subject. At the end of the 5 week down-titration period the sertraline group will return for a visit 14 between weeks 17 and 18 to return the study medication and to conduct a brief safety review. Those in the therapy group will be given up to 3 booster sessions during this 5-week time period. These sessions will serve as a wind-down from the therapy program and are designed to reduce sudden recurrence of anxiety symptoms due to an abrupt end of therapy.

At the end of week 24, the three month follow-up visit 15 phone call will be conducted with all subjects and/or parents, to collect additional behavioral assessments as well as follow-up on any unresolved adverse events if necessary.

Summary of Assessments

Subjects will include 132 children and their parents who will be randomly assigned during Phase 1 (44 per group) to CBT, sertraline, or placebo in a 1:1:1 allocation. Gate A is a 20-minute telephone screen to elicit preliminary inclusion/exclusion information (e.g. age, known diagnosis of ASD, signs/diagnosis of anxiety). The Gate B assessment involves collection of demographic information, a qualification assessment, and administration of pre-test measures including an fMRI scan for subjects able to travel to the UC Davis medical center. Subjects will be randomized in a 1:1:1 ratio to a treatment condition after completing the screening assessments if eligibility criteria are met to receive BIACA, SSRI or placebo.

At Gate B assessment, study staff will obtain informed consent from the parent, and assent from the child, if appropriate, either in-person or remotely utilizing Docusign. Consented youth will have a qualification and pre-test assessment consisting of behavioral/clinical assessments, neuroimaging, and dot probe task over the course of multiple days. Screening assessments will be completed within 60 days of informed consent being obtained and prior to randomization. Thereafter, patients will receive 16 weeks of CBT, sertraline, or placebo treatment. At end of week (EOW)16, visit 17, patients will complete the post-treatment assessment consisting of behavioral/clinical assessments, neuroimaging, and dot probe task as applicable. The sertraline and placebo groups will begin a five week down-titration and participate in a follow-up visit 18 at EOW 21. At visit 19 (week 28), patients will complete a 3-month phone follow-up assessment consisting of behavioral/clinical assessments and subjects randomized into the medication arm will be unblinded to treatment assignment and those in placebo group will be offered to continue into Phase 2 where they will be given their choice of either 12 weeks of CBT or sertraline treatment.

Neuroimaging (fMRI)*(Phase 1 and Training ICF):*

MRI Familiarization Play and Mock Scanner

The child will be introduced to the MRI scanner prior to the real MRI through 1-2 familiarization sessions at the UC Davis Imaging Research Center prior to the MRI scan. In the MRI familiarization session, each child will then be given the opportunity to become comfortable with the mock MRI first and then transition to the actual MRI scanner. Prior to arrival, study personnel will consult with parents to develop an individualized training plan for each child. This plan may include copies of the MRI sounds to listen to at home and collecting information about what would be the best motivators and rewards for the child (e.g., food, toys, iPad time). Each child will be given the opportunity to do 1-2 mock sessions in the practice MRI environment prior to transitioning to the real scanner. At the mock scan, the child will learn to lie still in the MRI bore while hearing scanner noises. We will utilize a potentiometer for monitoring movement and will employ a differential reinforcement plan to train children to lie still. Head movement can be measured with accuracy to 1 mm/sec, which can allow study personnel to provide immediate feedback on amount of motion. The movement criterion can be adjusted according to the child's current ability and gradually made more stringent as training progresses. The goal for each training session is to

incrementally increase the amount of time the child is able to lie still while the gradient noises are played. Through practice and conditioning, children will learn to control their body movement to be able to complete the MRI tasks.

Neuroimaging Protocol

MRI scans will be acquired on a Siemens 3T scanner at the UCD Imaging Research Center. For each child, the scanning protocol will consist of a structural scan (axial 3D SPGR/MPRAGE, 5 minutes), a modified Dot Probe task (described below; 10 minutes), a resting state (EPI-BOLD sequence; 10 minutes), and a phase map (2 minutes). The total time in the scanner for each child will be approximately 40 minutes, but additional time will be allowed to ensure the child has time to become familiar and comfortable with the environment and process.

If a subject is taking a stimulant medication, they will be asked not to take it for 48 hours prior to the fMRI session as it can affect the data we are collecting. Subjects will not be excluded from the study if they do not agree to this stimulant washout period; subjects may also consult with their physician prior to making a decision. MRI data may still be collected and its usability determined later.

The Dot Probe task done during the MRI will be a modified version of the behavioral Dot Probe task, designed by Dr. Susan Rivera. The task will be presented in one block consisting of 180 trials. The task begins with a 1-6 second central fixation cross, followed by a 500ms face pairing that is followed immediately by a 500ms asterisk probe appearing in the same spatial location as one of the previous faces. There are three categories of face pairings: angry paired with neutral, happy paired with neutral, and neutral paired with neutral. Expressions are modeled by twenty-eight different actors from the NimStim stimulus set [17]. Sex and race of the face as well as emotion and probe side are randomized. Scoring is conducted in the same manner as the behavioral version to determine trial congruency, average latency, and an overall bias score.

Dot Probe Task *(Phase 1 and Training ICF)*:

Dr. Susan Rivera's lab has carried out infrared eye-tracking experiments in TD children, children with autism and with FXS on a Dot Probe Task that was modified to be a completely passive viewing eye tracking task. The dot probe task, which measures selective attention to emotional stimuli, is presented in two blocks, each consisting of 40 trials. The task begins with a 1000ms central fixation cross, followed by a 500ms face pairing that is followed immediately by a 1500ms asterisk probe appearing in the same spatial location as one of the previous faces. There are three categories of face pairings: angry paired with neutral, happy paired with neutral, and neutral paired with neutral. Expressions are modeled by twenty-eight different actors from the NimStim stimulus set [17]. Sex and race of the face as well as emotion and probe side are randomized. A trial is identified as congruent if the probe appears in the same location as an emotional face had just appeared, and incongruent if it appears on the opposite side of the screen. Trial congruency is counterbalanced and randomized throughout the task. An overall bias score is calculated for each participant by subtracting the average latency to fixate to the asterisk probe on congruent trials from the average latency to fixate to the asterisk probe on incongruent trials. This task will be conducted in two versions, one will be done in the MRI scanner and the other will be done at the MIND Institute during the specified visits based on the appropriateness of the task for the participant and the discretion of the Principal Investigator.

Behavioral/Clinical Assessments:

Assessments will be performed remotely or at the MIND Institute by trained clinicians. Behavioral questionnaires may be provided to the family ahead of their visit to fill out at their convenience and return to the study team when they come in for their visits to help increase completion rates. Any assessments or study procedures deemed not appropriate for a subject based on their cognitive abilities and/or behaviors, the subject or their parent/caregiver's willingness to complete the assessment, and/or study staff's discretion will not be administered with the exception of those required for inclusion/ exclusion criteria and safety assessments. A list of the planned assessments in the battery that will be administered is provided below:

I. Behavioral Assessments:

a. List of Clinical Assessments used in STAAR

Assessment	Description	Duration	Completed By	Phase of Study
Anxiety Disorders Interview Schedule (ADIS) with Autism Spectrum Disorder Addendum (ASDD) [19, 20]	A semi-structured interview designed specifically for the diagnosis of anxiety and other related disorders in children and adolescents. Symptoms are judged as either present or not present based on DSM-V criteria. Impairment ratings are made by the children and parents using a 9 point scale (0-8). To issue a final diagnosis on the child and/or parent interview, the impairment rating for each diagnosis must be 4 or greater.	1.5 hrs.	Parent	Training Phase 1 Phase 2
Autism Diagnostic Interview (ADI-R)	Comprehensive interview provides a thorough assessment of individuals suspected of having autism or other autism spectrum disorders. clinical interviewer questions a parent or caretaker who is familiar with the developmental history and current behavior of the individual being evaluated. Used to confirm diagnosis in ASD group and to measure onset status (early onset, regression) (Lord et al, 2003).	3 hrs.	Parent	Training Phase 1 Phase 2
Autism Diagnostic Observation Schedule (ADOS-2) [25]	Ten social "presses" are scored for communication, reciprocal social behavior, and repetitive behaviors and stereotyped interest patterns. Lord et al. (2000)	.75 hrs	Child	Training Phase 1
Brief Observation of Symptoms of Autism (BOSA)	Parent or clinician administered standardized context of activities based off the ADOS and BOSCC which provides a tool to provide ADOS scoring codes.	.25 hrs.	Child	Training Phase 1
Childhood Autism Rating Scale-2 (CARS-2)	Clinician administered behavioral rating scale used for assessing the presence and severity of symptoms of autism spectrum disorders based on direct observation.	.25 hrs.	N/A	Phase 1
Clinical Global Impression (CGI)[31]	Set of clinician ratings to assess overall severity of an individual's symptoms as well as changes in functioning over time. Raters make two ratings using a seven-step categorical scale: 1) Clinical Global Impression- Severity (CGI-S): An initial assessment of the severity of illness within the last week; and 2) Clinical Global Impression- Improvement (CGI-I): Global improvement from the baseline CGI-S.	.25 hrs.	Parent	Phase 1 Phase 2
Cognition Battery of the NIH Toolbox	The NIH Toolbox Cognition Battery is a computerized task used to assess the participant's cognition across five different domains: Executive Function and Attention, Episodic Memory, Language, Processing Speed, and Working Memory. The battery has seven subtests ranging from 3 to 7 minutes each. Scores on each subtest can be combined to form a cognitive function composite score.	.5 hrs.	Child	Phase 1
DSM-5 Checklist	A short interview with parent about the child's history of ASD symptoms. The interview will be based on a DSM-5 symptom checklist.	.25 hrs.	Parent	Phase 1
Edinburgh Inventory Handedness Assessment	The EDI is a short scale used to assess a participant's handedness. Items are reported by direct observation of the participant's behavior or by parent report of the behavior.	.25 hrs.	Child	Phase 1
Impact of COVID-19 on Anxiety Scale (COVID)	A brief subject/caregiver rating from -3 to 3 of a participant's anxiety level during to the COVID-19 pandemic. The rating will	.25 hrs.	Parent	Phase 1 Phase 2

	assess the overall impact of the pandemic on a participant's anxiety.			
NIH Toolbox Emotional Battery	A computerized series of questionnaires along a series of subscales including Positive Affect, General Life Satisfaction, Emotional Support, Friendship, Loneliness, Perceived Rejection, Perceived Hostility, Self-Efficacy, Sadness, Perceived Stress, Fear, and Anger. For ages 18+, the battery also includes surveys of Meaning and Purpose and Instrumental Support.	.5 hrs.	Parent	Phase 1 Phase 2
Pediatric Accomodation Scale (PAS)	Measure designed to be administered by a trained clinician familiar with the child's anxiety symptoms. Responses should be chosen based on clinician judgment of parent report. Each item contains examples that may be substituted with a child's specific symptoms. After each item, the clinician may ask follow-up questions to clarify or to probe more closely for accommodation. Clinician responses should be based on frequency and severity/interference of the accommodation behavior in question, rather than the associated anxiety symptom. The item response format is: 0 (Never), 1 (Rarely), 2 (Occasionally), 3 (Often) and 4 (Always.	.25 hrs.	Parent	Phase 1 Phase 2
Subjective Units of Distress Scale (SUDS)	Short clinician rating scale from 0-7 of a participant's distress during the study required blood draws. The rating will assess changes or improvements with repeated exposures throughout study participation.	.25 hrs.	N/A	Phase 1 Phase 2
The Pediatric Anxiety Rating Scale (PARS) [21]	Assesses anxiety symptoms and the associated severity and impairment in children over the past week. The Symptom Checklist consists of 50 items assessing 6 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 ASD.	.75 hrs	Parent	Training Phase 1 Phase 2
Wechsler Abbreviated Scales of Intelligence (WASI)	General cognitive ability measure used to assess specific and overall intelligence. The Vocabulary and Similarity subtests yield a verbal IQ score, and the Block Design and Matrix Reasoning subtests yield a performance IQ scoreThe 2-Scale version of the WASI will be used to minimize subject burden.	0.5 hrs.	Child	Training Phase I
Youth Top Problems (YTP)	Structured assessment of primary concerns to be addressed in treatment. Open-ended measure that identifies the 3 problems of greatest concern to parents at pre-treatment and then are rated on the severity of those problems weekly during treatment.	.25 hrs.	Parent	Phase 1 Phase 2

b. List of Questionnaires used in STAAR

Assessment	Description	Duration	Completed By	Phase of Study
Adaptive Behavior Assessment System, Third Edition (ABAS-3)	A parent report questionnaire that gives the researcher a complete picture of functional skills across the life span. The ABAS-3 covers three broad domains (conceptual, social and practical) and 10 skill areas. On a 4-point response scale, raters indicate whether, and how frequently, the individual performs each activity. The questionnaire will be completed using an iPad.	.25 hrs.	Parent	Phase 1 Phase 2

COVID-19 Adolescent Symptom & Psychological Experience Questionnaire (CASPE)	Parent report questionnaire capturing information around COVID-19 pandemic affecting the child.	.25 hrs.	Parent	Phase 1 Phase 2
Child Behavior Checklist (CBCL) [29]	For children 6 – 18 years old. Provides ratings of behavioral, emotional, social, affective, anxiety, somatic, attention deficit hyperactivity disorder, oppositional defiant, and conduct problems.	.25 hrs.	Parent	Phase 1 Phase 2
Children's Alexithymia (ACQ)	A 20 item questionnaire that represents three factors: Difficulty identifying feelings, Difficulty describing feelings, and Externally oriented thinking. The item response format is: not true, a bit true, true.	.25 hrs.	Child	Phase 1
Children's Response Style Questionnaire (CRSQ)	Uses 25 items clustered into the three general response styles of rumination, distraction, and problem solving. Children are asked to rate how frequently they respond to a sad mood with the particular response. A higher score indicates a more frequent use of that response style.	.25 hrs.	Child	Phase 1 Phase 2
Children's Sleep Habits Questionnaire (CSHQ)	A brief questionnaire to assess common sleep behaviors in children.	.25 hrs.	Parent	Phase 1 Phase 2
Conners 3rd Edition-Parent Short Form (Conners 3-P(S))	This instrument is designed to assess Attention Deficit/Hyperactivity Disorder (ADHD) and its most common co-morbid problems in children and adolescents aged 6 to 18 years old. When used in combination with other information, results from the Conners 3–P(S) can provide valuable information for guiding assessment decisions. This report provides information about the parent's assessment of the youth, how he/she compares to other youth, and which scales are elevated.	.25 hrs.	Parent	Phase 1 Phase 2
Consumer Satisfaction Questionnaire	A 14-item questionnaire designed to measure parents' evaluation of and satisfaction with the treatment program received since joining the study. Includes 11 Likert scales to assess satisfaction and 3 opportunities to collect open-ended responses or provide additional comments.	.25 hrs.	Child Parent	Phase 1 Phase 2
Demographic & Background Information Form	This form collects data regarding the participant's racial and socioeconomic status including factors of education, occupation, sex, and marital status.	.25 hrs.	Parent	Phase 1
Emotion Regulation Questionnaire (Emotion)	A 10-item scale designed to measure respondents' tendency to regulate their emotions in two ways: (1) Cognitive Reappraisal and (2) Expressive Suppression. Respondents answer each item on a 7-point Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree).	.25 hrs.	Child	Phase 1 Phase 2
Expectancy Rating Questionnaire (ERQ)[33]	The expectancy questionnaire is a simple scale that is administered for measuring treatment expectancy and rationale credibility after the participant completes the experiment.	.25 hrs.	Child	Phase 1
Hierarchical Personality Inventory for Children (HiPIC)	Comprised of 144 short statements about the child to be rated by parents or teacher scored on 5-point Likert scales ranging from very untypical (1) to very typical (5). Assesses the domains extraversion, benevolence, conscientiousness, emotional stability (reversed to neuroticism) and imagination. In addition, the HiPIC is scored on 18 facets composed of 8 items each, which are summed and averaged to obtain the domains. The	.25 hrs.	Parent	Phase 1

	number of facets is four for extraversion, five for benevolence, four for concentration and two and three for neuroticism and imagination.			
Multidimentional Anxiety Scale for Children (MASC-II)	Questionnaire used to provide comprehensive assessment of anxiety dimensions in children and adolescents aged 8-19 years.	.25 hrs.	Parent	Phase 1 Phase 2
Parent Expectancy for Treatment (PETS)	Measures parent expectancies for therapy and pretreatment assessed prior to the first therapy session. The measures are completed by the parent of referred children. 25-item questionnaire measure with 1-5 scale Likert rating response format.	.25 hrs.	Parent	Phase 1 Phase 2
People In My Life (PIML)	A 47 item self-report measure of attachment to parents and peers that is modeled after the IPPA (Armsden and Greenberg, 1987). PIML provides scores on three specific dimensions (Trust, Communication, and Alienation) which are combined into a summative Attachment score.	.25 hrs.	Child	Phase 1 Phase 2
Perseverative Thinking Questionnaire- Child Version (PTQ-C)	A 15-item self-report questionnaire that measures content-independent repetitive negative thinking (Bijttebier et al., 2015). Participants rate items on a 5-point scale (“never”, “almost never”, “sometimes”, “often”, “almost always”). The PTQ-C is highly correlated with disorder-specific measures of repetitive negative thinking such as rumination and worry and is associated with symptoms of anxiety and depression. However, it is designed to assess repetitive negative thinking in children transdiagnostically.	.25 hrs.	Child	Phase 1 Phase 2
Peterson Development Scale Parent Report (PDS)[30]	Used to assess pubertal status of the participants. Parents of participants will be asked to fill out a slightly modified Parent Report version. It is valid for assessing meaningful differences in relative stage Tanner stage acquisition across child and adolescent participants in research samples.	.25 hrs.	Parent	Phase 1 Phase 2
Repetitive Behavior Scale-Revised RBS-R [27]	A 43-item scale asking participants to rate how much of a problem repetitive behaviors are on a scale ranging from 1 to 100 (1 = not a problem, 100 = a huge problem). The rater also decides to what extent the behavior is a problem for the person as well as for the people around him or her. A Global Severity Score is produced for the individual. Insistence on sameness also can be rated using this measure.	.25 hrs.	Parent	Phase 1
Revised Children’s Manifest Anxiety Scale (RCMAS-2) [22]	A 49 item scale used to measure the level and nature of anxiety experienced by the child. Participants respond to each item using a yes/no format, with higher scores indicating higher levels of the construct being assessed. The two constructs are anxiety and defensiveness. The assessment yields a total anxiety score as well as three anxiety subscale scores: Physiological anxiety, worry, and social anxiety.	.25 hrs.	Child	Phase 1 Phase 2
Scahill Measure of Anxiety (PRAS-ASD)	A 25-item measure that the parent fills out to describe the child's worries and anxiety-related behaviors in the past two weeks. The items are measured from None (0), Mild (1), Moderate (2), and Severe (3). Valid for lower-functioning participants.	.25 hrs.	Parent	Phase 1 Phase 2
School Quality (Dwyer)	Questionnaire used to document subject’s schooling type and history, along with parent assessment of child’s experience in school.	.25 hrs.	Parent	Phase 1

Service Assessment for Children and Adolescents	We ask parents to provide a brief record of the services their children have received including ABA therapy, speech and language therapy, social skills therapy, physical therapy, special education and occupational therapy.	.25 hrs.	Parent	Phase 1 Phase 2
Sibling Inventory of Behavior (SIB)	A 32-item parent measure that evaluates attitudes of typically developing children towards their sibling with ASD. It includes (a) a 5-item empathy/concern scale, (b) a 6-item companionship/involvement scale, (c) a 6-item rivalry scale, (d) a 5-item conflict/aggression scale, (e) a 5-item avoidance scale, and (f) a 4-item teaching/directiveness scale. Each item is answered on a 5-point Likert scale, ranging from 1 (never) to 5 (always).	.25 hrs.	Parent	Phase 1 Phase 2
Social Communications Questionnaire (SCQ)	A parent measure used to confirm a preference of ASD diagnosis; studies have supported use in children greater than 4 years (Rutter et al, 2003).	.25 hrs.	Parent	Phase 1
Social Responsiveness Scale (SRS) [24]	A 65-item scale used to assess autism symptom severity. Subscales include: Social awareness, social cognition, social communication, social motivation, & autistic mannerisms. A T-score of 60 constitutes a clinical cutoff. Social awareness can be rated on this instrument	.25 Hrs.	Parent	Phase 1
The Anxiety Depression and Mood Screen (ADAMS)	Parent report questionnaire that serves as a screening instrument to determine anxiety, mood, and depression among individuals with intellectual disability. The respondent is asked to rate the extent to which their child displays target symptoms.	.25 hrs.	Parent	Phase 1 Phase 2
Therapist Alliance Scale – Child and Parent Reports (TASC – R Child/Parent) [32]	The Therapist Alliance Scale for children and parents is a 12 item scale completed by the child and the parent. Items are rated on a 4 – point scale ranging from 1 (not at all) to 4 (very much). There is strong internal consistency of these parent-reports of the child-therapist alliance.	.25 hrs.	Child Parent	Phase 1 Phase 2
The Stress Survey Schedule for Individuals with Autism and Other Pervasive Developmental Disabilities (SSS)	A tool to increase awareness of environmental stressors that affect the lives of persons with autism. Used to create programming aimed at modifying stress reactions in the population of persons with autism, thereby enhancing the quality of their lives and their overall physical and emotional well-being. 62-item parent measure.	.25 hrs.	Parent	Phase 1 Phase 2

II. Medical/Safety Assessments

Safety measures will be conducted at the Phase 1 initial screening visit, including vital signs, safety labs, review of systems, medical history, and electrocardiogram if indicated to verify inclusion and exclusion study criteria. An electrocardiogram will be administered for subjects who are not followed regularly by a health care provider or have a history of heart or blood pressure issues. The safety labs, listed in the table below, will include a CBC: complete blood count, CMP: complete metabolic panel, TSH: thyroid stimulating hormone, and Pregnancy testing. The pregnancy testing will only be conducted on female participants of child-bearing potential via a urine pregnancy test. The vital signs measures to be collected include weight, height, head circumference, temperature, blood pressure, and pulse. The safety measures will be carried out either through the UC Davis health system pathology laboratory, a Quest laboratory location, UCLA Clinical and Translational Research Center, or on-site at the MIND Institute clinic.

The subjects randomized to the Phase 1 active or placebo medication cohorts will have vitals and a review of systems conducted at visits 1 through 17. Safety labs will be repeated at follow-up visit 9, and at additional timepoints throughout treatment at the discretion of the study doctor if indicated. The Phase 2 medication cohort will also have vitals and a review of systems conducted at visits 2 through 14 and safety labs repeated at follow-up visits 7, and at additional timepoints throughout treatment at the discretion of the study doctor if indicated. The safety labs conducted at the follow-up visits will include a CBC: complete blood count, CMP: complete metabolic panel, and Pregnancy testing (if applicable). The subjects randomized to the therapy cohort under Phase 1 or Phase 2 will not undergo any of the safety or medical assessments at any of the follow-up visits.

Safety Lab Tests

Chemistry (CMP)	**Hematology (CBC)**	**Thyroid**	**Urinalysis**
Sodium	Hemoglobin	TSH	Pregnancy spot urine
Potassium	Hematocrit		
Chloride	WBC		
Carbon Dioxide	RBC		
BUN	MCV		
Creatinine Serum	MCH		
Glucose	MCHC		
Calcium	RDW		
Protein	MPV		
Albumin	Platelet Count		
ALP	Neutrophils		
AST	Lymphocytes		
ALT	Monocytes		
Bilirubin Total	Eosinophil		
	Basophils		

The schedule of procedures is also listed in a table format below for both Phase 1 and Phase 2:

	Screening	Phase 1: Treatment Period (Therapy or medication or placebo)																	Follow-Up
Evaluation	V1 (wk 0)	V2 (wk 1)	V3 (wk 2)	V4 (wk 3)	V5 (wk 4)	V6 (wk 5)	V7 (wk 6)	V8 (wk 7)	V9 (wk 8)	V10 (wk 9)	V11 (wk 10)	V12 (wk 11)	V13 (wk 12)	V14 (wk 13)	V15 (wk 14)	V16 (wk 15)	V17 (wk 16)	V18 (wk 21)	V19 (wk 28)
Informed Consent	X																		
Inclusion/ Exclusion	X																		
Dx Confirmation	X																		
Medical History	X																		
Con Med/Therapy Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*	X**
Review of Systems	X	X*	X*	X*	X*		X*		X*		X*		X*		X*		X*	X*	
Suicidality Screen	X	X*	X*	X*	X*		X*		X*		X*		X*		X*		X*	X*	
AE Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*	X**
CGI-S	X																		
CGI-I					X				X				X				X		X
Dose Review/Titration		X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*		
Vital Signs[1]	X	X*	X*	X*	X*		X*		X*		X*		X*		X*		X*	X*	
EKG	X																		
Safety Labs	X								X*										
SUDS	X								X*								X*		
Urine Pregnancy	X								X*										
Research Labs	X																		
Randomization	X*																		
Dispense Study Drug	X*		X*		X*		X*		X*		X*		X*		X*		X*		
Drug Account.		X*	X*	X*	X*		X*		X*		X*		X*		X*		X*	X*	
fMRI[1]	X																X		
Dot Probe[1]	X																		
WASI	X																		
ADAMS	X																X		
ADOS-2[2]	X																		
ADIS/ASDD	X																X		
ADI-R	X																		
BOSA	X																		
CARS	X																		
PARS	X				X				X				X				X		X
DSM-V Checklist	X																		
NIH Toolbox (Emo)[1]	X																X		
NIH Toolbox (Cog.)[1]	X																		
RCMAS-2	X																X		
SRS-2	X																		
RBS-R	X																		
CBCL	X																X		
TASC-R C/ P		X			X				X				X				X		
ERQ		X			X														
PDS	X																X		
Edinburgh	X																		
ABAS-3	X																X		
Conners 3-P(S)	X																X		
COVID[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CASPE[3]	X																X		
Background Info	X																		
ACQ	X																		
HiPIC	X																X		
CSHQ	X																X		
Emotion	X																X		
PRAS-ASD	X																X		
Services Ass	X																X		
School Quality	X																		
YTP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PAS	X																X		
CRSQ	X																X		
MASC-II	X																X		
PETS		X																	
SSS	X																X		
PIML	X																X		
PTQ-C	X																X		

SCQ	X																		
SIB	X																X		
Satisfaction																	X		

* Designates items only being conducted for the subjects randomized into the active or placebo medication groups

** Designates items being assessed only if follow-up needed from post visit 17

[1] Assessment will only be conducted at office visits, will not be done if remote visit

[2]Assessment administration can be postponed to a later visit during the treatment phase if documentation of ASD diagnosis is available

[3] Assessment will only be administered during COVID-19 pandemic duration

		Phase 2: Follow-Up Treatment Period (Therapy or sertraline)													Follo w-Up
Evaluation	V1 (Phase 1 V19)	V2 (wk 1)	V3 (wk 2)	V4 (wk 3)	V5 (wk 4)	V6 (wk 5)	V7 (wk 6)	V8 (wk 7)	V9 (wk 8)	V10 (wk 9)	V11 (wk 10)	V12 (wk 11)	V13 (wk 12)	V14 (wk 17)	V15 (wk 24)
Con Med/ Therapy Review	X**	X	X	X	X	X	X	X	X	X	X	X	X	X*	X**
Review of Systems		X*	X*	X*	X*		X*		X*		X*		X*	X*	
Suicidality Screen		X*	X*	X*	X*		X*		X*		X*		X*	X*	
AE Review	X**	X	X	X	X	X	X	X	X	X	X	X	X	X*	X**
CGI-I	X				X				X				X		X
Dose Review/ Titration		X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*		
Vital Signs[1]		X*	X*	X*	X*		X*		X*		X*		X*	X*	
Safety Labs							X*								
SUDS							X*						X*		
Urine Pregnancy									X*				X*		
Dispense Study Drug			X*		X*		X*		X*		X*		X*		
Drug Account.		X*	X*	X*	X*		X*		X*		X*		X*	X*	
ADAMS													X		
PARS	X				X				X				X		X
ADIS/ASDD													X		
NIH Toolbox (Emo.)													X		
RCMAS-2													X		
CBCL													X		
TASC-R C/ P		X			X				X				X		
ERQ		X			X										
PDS													X		
ABAS-3													X		
Conners 3-P(S)													X		
COVID[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CASPE[2]													X		
CSHQ													X		
Emotion													X		
PRAS-ASD													X		
Services Assessment													X		
YTP		X	X	X	X	X	X	X	X	X	X	X	X		
PAS													X		
CRSQ													X		
MASC-II													X		
PETS		X													
SSS													X		
PIML													X		
PTQ-C	X												X		
SIB													X		
Satisfaction													X		

* Designates items only being conducted for the subjects randomized into the medication group

** Designates items being assessed only if follow-up needed from phase 2 visit 14

[1] Assessment will only be conducted at office visits, will not be done if remote visit

[2] Assessment will only be administered during COVID-19 pandemic duration

Data & Specimen Management & Confidentiality

We will utilize the Data Management and Statistics (DMS) Core of the Center, which will provide a complete informatics infrastructure to support the project and to ensure the highest level of data integrity at every step between data collection and data analysis. This infrastructure is achieved through three broad aims:

- **Aim 1:** To ensure that the data for each Center project meets best practice standards through data consolidation and the provision of accurate data collection and capture tools, automated scoring and processing procedures, and thorough ongoing data validation.
- **Aim 2:** To provide a highly efficient means for successfully conducting all proposed project analyses through the design and implementation of centralized data storage, data set preparation and reporting, and data transfer and dissemination.
- **Aim 3:** To provide state-of-the-art statistical support for all of the analytic goals of the proposed Center projects through close collaboration with the existing Biostatistics Core of the MIND Institute Intellectual and Developmental Disabilities Research Center (IDDRC, U54 HD079125).

The DMS Core will leverage many of the data entry systems that are currently in use for the existing APP longitudinal data. These systems involve robust ACCESS database data entry forms that have been programmed and maintained in Visual Basic by Dr. Young. Importantly, the data entry front-end systems require double data entry and include valid value range enforcement, thereby greatly limiting the introduction of any significant error into the data through data entry. Moreover, new data entry forms and respective data tables, with all attendant double entry and validation enforcement, can easily be auto-generated from metadata (i.e., codebooks) using Dr. Young's existing programming. These same front-end systems can also be used for study tracking and subject tracking of complex longitudinal study designs. These systems are then linked to their respective relational database tables, housed on secure remote network servers (e.g., MySQL) via open database connectivity (ODBC) protocols.

The DMS core will provide support for the existing web-based REDCap system used for ongoing data capture certain phenotypic data (e.g., medical records, chart reviews, etc.) in the APP. The REDCap system, housed in a separate data center at UC Davis Health System, provides data entry with double-entry and value validation, as well as a standard Application Programming Interface (API) that allows direct communication between external software (e.g.R) and the REDCap data.

The DMS will provide support for pre-processing of all collected data, including automated scoring, data reduction and aggregation, and data formatting. Specifically, as a way to increase the reliability and validity of collected data, the DMS will write and maintain programming scripts that can be run on all raw data. For example, data entry systems will require item level data on standardized tests such as the ADOS or anxiety assessments. Automated scoring programs will be utilized to standardize all calculations of total and domain scores, thereby reducing human error. Similarly, for subject level data such as eye-tracking data consisting of raw sample-level data (~100 samples per second), programming scripts can be developed to automate calculations of all dependent variables (e.g., fixations per stimulus).

The DMS will work to ensure that all data systems are secure by enforcing authorization for all access to the data. All centralized data storage will be accessible only by Center personnel with approved access who have undergone training in confidentiality and HIPAA compliance. Moreover, data with personal health information (PHI) will be stored separately from all other data and will only be accessible to the project manager. Data consolidation programming will never include PHI data by design such that all archived consolidated data and all data sets prepared for and used in data analyses will be de-identified. All data systems, including data collection and data capture systems, as well as centralized consolidated data will be backed up regularly to ensure that all data is recoverable and cannot be lost

The DMS will design and implement a data portal that will be available to all authorized Center Investigators and Biostatisticians. The data portal will be a web based system that will be implemented on the data server (described

above). The server will run MySQL server and Shiny Server Pro (see http://shiny.rstudio.com/articles/shiny-server.html) which provides the ability for users to run web-based applications in R to select and query data, visualize data, obtain descriptive statistics, and create customized datasets for download and further analysis. R is an open-source statistical programming language that is commonly used in all manners of data analysis and data management. Dr. Young has written a large number of R applications using Shiny in order to consolidate, manage, and query the existing APP data and to communicate with relational databases for archival purposes. These same applications will be deployed on the server space using Shiny Server Pro to facilitate access to the curated consolidated data in MySQL, which will also exist on the server space. Additional web-based software available for specific types of data exploration, such as *Phenotips* used for phenotyping, might also be implemented on the same server for exploring consolidated data.

Identifying information, such as name, address, SSN, will not be accessible to anyone outside the project staff. SSN is required in order to provide and process compensation payments to participants by the Department of Psychiatry and Behavioral Sciences. SSNs collected will not be used for any other purpose and will be protected in the same manner as all other Personal Health Information (PHI). Analytical databases containing PHI will be maintained on UCDMC servers, protected by UCDMC maintained firewalls. The PHI will not be stored on mobile electronic devices (flash drives, laptops, desktop computers) as per UCDMC policy. All guidelines for HIPAA will be followed and subjects will be informed about HIPAA prior to signing the research authorization form during the consent process. The personal identifier information and the assigned unique identifier number for each child will be kept in separate databases. Clinical assessment, diagnostic, lab (archived samples & assay values) and questionnaire data will be entered into and archived in a separate database for later analysis. Only the unique identifier number will be included with the demographic, clinical assessment, diagnostic questionnaire data, as well as brain images and specimen. The paper or hard files that include the personal identifier, clinical, and assessment data for all study children will be kept in a secure medical records area at the MIND Institute for the duration of the study. Recordings of testing sessions will be secured in locked file cabinets and only accessible by research staff or stored on secure servers. Recordings of subject who do not meet study criteria will be kept for scoring and reliability purposes, labeled with participant ID number and stored in same manner as all other recordings of participants. At the end of the study, all personal identifier information will be eliminated from the hard copy files. The personal and family data and information derived from this study will not be disclosed to any other agency, party, or individual without the expressed written permission for release of the information from the parent or guardian. No identifiers, used for recruitment purposes, will be disclosed to a third party except as required by law or for authorized oversight of the research project or funding sponsor.

NDAR

The funding sponsor for this study has a requirement for the sharing of data collected in the study with the National Database for Autism Research (NDAR). NDAR is a biomedical informatics system and data repository, created by the National Institutes of Health to assist biomedical researchers working to develop a better understanding of autism and/or to develop more effective methods to diagnose, treat and prevent autism spectrum disorders. NDAR does have a Certificate of Confidentiality for data in the repository. All data shared within NDAR uses a Global Unique Identifier (GUID) for each study participant and allows researchers to share data without exposing personally identifiable information. As provided by NDAR, UC Davis personnel utilize the GUID Tool, a free customized software application, to generate the GUID for each study participant. All personally identifiable information remains on UCMDC servers protected by firewalls. In order to generate this GUID identifier, parents of participating children will be asked to provide the child's city of birth, in addition to standard study data (child's legal name and date of birth). Therefore, no personally identifying information is shared with NDAR. The investigators assure the IRB that participants' health information will not be disclosed to third parties except as required by law and to the sponsor's monitors as mentioned above. NDAR has generated a brochure that will be given to parents of participating children and explains what NDAR is and what it means.

Specimens

Blood samples for exploratory research measures will be collected at the screening visit 1, not exceeding 21ml, in the form of one 4ml EDTA tube and two 8.5ml yellow top citrate tubes, and will be banked using identical procedures as the originating study, Autism Phenome Project. Collected specimens will be indexed and stored at the MIND Institute Biosciences Building with oversight by the Project Manager. Blood specimens will

be distributed by the Project Manager and staff to several local and national collaborative projects. Each transfer will be initiated after appropriate research distribution agreements have been processed.

Genetics and Genomics Projects: The goal of the Genetics and Genomics projects is to identify molecular signatures that correlate with the autistic phenotype. Peripheral blood samples drawn from the enrolled subjects (and parents) will be used to isolate DNA and RNA. With the RNA, comprehensive gene expression studies using the Affymetric microarray technology will be performed in order to identify specific molecular signatures that may be able to predict the autistic phenotype. DNA will be used to screen the entire genome for gains or losses of segments of the DNA in order to determine if these correlate with the autistic phenotype. DNA from families where a complete trio can be obtained (DNA from subject and both biological parents) will be sent to the Autism Speaks MSSNG project for whole genome sequencing. MSSNG is a program sponsored by Autism Speaks to create the world's largest genomic database on autism. The initial goal of MSSNG is to sequence the DNA of over 10,000 individuals from families affected by autism and provide the whole genome sequence data along with the phenotype description to the researcher community in a cloud environment (the "MSSNG Database") for research and analysis. It is the policy of MSSNG to provide the research community with a centralized resource to test hypotheses without duplicating collection and sequencing efforts. The data in the MSSNG Database will be made available to authorized researchers on-line using the Google Cloud or a similar platform. Researchers will be allowed to not only perform research and analytics on the secure Google platform, but may also be permitted to download, extract, and/or copy data from the MSSNG Database and retain and store copies of data in their own information technology systems. Researchers have emphasized on numerous occasions the significant expansion of research capabilities that would be afforded by enabling researchers to download data from the MSSNG database. Through MSSNG, authorized researchers will have access to a large database of whole genome sequence data on thousands of autism cases, which will speed discovery of autism etiology and possible treatment options.

All specimens will be given a numeric code (barcoded) and will be free from any personal identifiers. No laboratory personnel will have access to any information that could potentially identify a study participant.

All requests for materials must be sent through Project Manager then to Principal Investigator for approval. All research personnel may obtain data or specimens as approved by PI.

Withdrawal

Participants may withdraw from the study at any point without repercussion from the study team. The data and biological specimens collected prior to their withdrawal may continue to be used for analysis.

Adjunctive Services and Attrition Prevention (ASAP)

It is not possible to define a priori all possible situations that may require adjunct services during the course of a trial. To insure our study will be comparable to others in the literature with respect to uniformity of practices, we will utilize a strategy implemented in other large federally funded multisite comparative RCTs (e.g., CAMS, TADS). To address subject crises or unusual needs/circumstances that arise during our trial, additional treatment sessions (i.e. ASAP sessions) are provided to address these needs and facilitate subject retention. A maximum number of sessions are allowed for each phase of the study (Intake: 1; Acute Treatment Phase: 2; Follow-up Phase: 2). Subjects who require more than this limited intervention will be prematurely terminated as defined below.

Premature termination and dropping out

At any time, subjects may deteriorate or develop clinical crises that lead the site team to recommend additional out of protocol treatments above and beyond that provide by ASAP session described above. Such "prematurely terminated" subjects may continue to be treated within their assigned treatment arm (as long as this does not pose a danger of contaminating the treatment of other subjects in that arm) and we would continue to collect assessments. Subjects who are prematurely terminated are to be distinguished from "drop outs", defined as subjects who refuse to furnish further data or who refuse study treatment or both. Stated differently, dropouts are

defined as those subjects who withdraw consent to participate while premature terminators are defined as subjects for whom treatments require supplementation and are therefore withdrawn by the study team. Study drops out will be encouraged to return for a last assessment, which would then be followed by end-of-treatment recommendations. Several procedures will be used to reduce attrition, including setting clear expectations about the research process, provision of free clinical services and compensation for assessments, and the availability of MIND Institute child life undergraduate students who provide supervision for siblings during sessions.

In addition, the study PI may choose to remove a subject from the study due to non-compliance with study protocol, new information presented that changes subject eligibility (i.e., parent has failed to report on an eligibility criterion accurately), or study participation places undue burden on the subject and/or their family. At this time, the study team will review with the family non-study options that may better meet their's child's needs.

Concomitant medications

Subjects may also require new pharmacologic intervention for routine pediatric illness at various time points during the study given its duration, which may be up to 20 weeks. Given that concomitant medications could interact with sertraline pharmacokinetically and/or pharmacodynamically, we will take special precaution in instructing parents/legal guardians on the importance of recording and reporting use of all medications both prior to and during study participation. The more common pediatric medications will be classified as acceptable or unacceptable, and this list will be given to all research staff as well as parents/legal guardians. Medications not on the list will be discussed between the study physician and parent/legal guardian or subject‘s pediatrician prior to administration. Special attention will be given to nonpsychotropic drugs with known interactions with sertraline. Subjects with serious medical illness requiring treatment will not be enrolled.

Potential Risk to Subjects & Measures to Protect Against Risk

The risks of participating in this project include relatively lengthy psychiatric evaluations, participating in psychotherapy or taking the medications (placebo and sertraline). As detailed below, “Protection Against Risk,” our adverse events monitoring strategy includes an initial screening by the project coordinator, followed by detailed assessment by Dr. Pakyurek to assure uniform ascertainment of side effects in each treatment arm. The treating clinician reviews the adverse event report and documents the adverse event, its severity and association with study treatments, and all actions taken by the study team. Similar to CAMS, we will provide training in the collection and coding of adverse events at the study start-up meetings to standardize data collection and maintain quality assurance of these procedures for all clinicians.

Assessment-related distress

Discomfort associated with the psychiatric evaluation and administration of rating scales – either due to the discussion of subjectively difficult topics, or due to the length of time required for the interviews and questionnaires. However, with regard to potential discomfort, our experience indicates that most people welcome the opportunity to discuss their experiences with a trained clinician; and any information shared by the subject will be kept confidential. We recognize that child participants must complete a number of measures that were chosen to assess a range of constructs that we believe may be impacted by the intervention or help understand (i.e., moderate) treatment outcome. Breaks will be given as much as possible to decrease boredom and physical/psychological discomfort. As well, we will compensate families for the Pre-test, Post-test, and 3 month follow-up assessments.

Therapy-related distress

Increased anxiety and subjective distress is commonly acknowledged as an appropriate and expected reaction to psychotherapies aimed at anxiety reduction. This effect is usually very transitory and mild, and is thought to be a result of the patient gradually stopping his or her avoidance of anxiety provoking situations while simultaneously allowing one‘s self to approach and/or think about these situations. If noted or described to the therapist (e.g., on CBT homework forms, during the course of discussion), this effect of treatment will not be described as an adverse event. The exception to this would be cases whereby a subject or parent specifically describes the reaction as an

adverse effect of participation. In such cases, CBT therapists can make certain adjustments to the pace or intensity of therapy (e.g., do a simpler exposure exercise; conduct further cognitive work before proceeding to exposure; do guided, therapist-assisted exposures) until the patient is ready to or asks to approach the anxiety-provoking stimuli again.

Placebo outcomes

Symptoms possibly may not improve or may worsen, if a subject receives placebo. Participants have the right to withdraw from the study at any time. We will implement very strict rescue criteria should a child's symptoms worsen significantly, they require a higher standard of care (i.e., inpatient), and/or they experience suicidality or significant side effects. Should a participant's symptoms markedly worsen, and/or they experience suicidality or significant side effects, s/he will be immediately withdrawn from the study and provided with the standard of care, which may include hospitalization, if necessary. Drs. Pakyurek, Solomon, and Winder-Patel will be available at all times to study participants in the event of a clinical emergency; both this availability and how to reach the investigators in an emergency will be clearly communicated orally and in writing to study participants. All study interventions will be provided free of cost. Although not specifically approved by the FDA for the treatment of anxiety in youth with ASD who are studied in this protocol, sertraline is a commonly used medication in adults and children for depression, anxiety, and OCD, and is FDA approved in children and adolescents with OCD as young as age 6 years. It has also been used in pilot studies in children and adolescents with ASD, as well as often in neurotypical youth with anxiety disorders. In addition, the drug has a high index of safety and is rarely associated with serious side effects. To insure participant and others safety, medication will be provided in childproof containers with the currently FDA approved sertraline Medication Guide.

Side Effects of Sertraline

Subjects usually tolerate sertraline well and most of the side effects are mild, transient and/or responsive to dose reduction. Commonly occurring side effects for sertraline consist of gastrointestinal symptoms (nausea, cramps, diarrhea, lack of appetite), central nervous system symptoms (increased motor activity, jitteriness), insomnia, headaches, tremor and occasionally tiredness. Some subjects become disinhibited demonstrating silliness or giddiness. Antidepressants as a group may trigger mania/hypomania in vulnerable subjects. However, to minimize this from occurring, bipolar disorder (history of mania or hypomania) will be an exclusion to enter this project. Other side effects are much less common.

In the event of a moderate or severe adverse reaction to the medication, the medication will be reduced or withdrawn and clinical staff will follow the patient closely until the adverse reaction remits. In the event of minor side effects (e.g., mild headaches), the medication may be maintained at the current dose levels or reduced. We also take seriously the recent action by the FDA to require (1) a —black box warning regarding the development of suicidality early in the course of treatment with antidepressants (2) the provision of an FDA approved Medication Guide with each filled prescription, and (3) the need for a monitoring plan for symptom worsening or suicidality. These requirements will result in our using specific wording in the consent process and appropriate preparation of the protocol (see below). We will incorporate the specific language noted by the FDA for sertraline into the current consent forms. In addition, in order to be consistent with the FDA proposal, we will discuss the study dosing with each family as part of informed consent and present it in written form to the family when each prescription is filled at the site's pharmacy. Also, we use a monitoring schedule that is consistent with the plan suggested in the FDA approved labeling for sertraline (i.e. weekly contact for the first 4 weeks and then biweekly thereafter with phone check-ins). The research team is available 24 hours per day in the case of medical emergency or serious adverse events. If at any point in the treatment trial the treating clinician determines that a patient's symptoms have become sufficiently distressing or dangerous, the patient will be withdrawn from the study and other treatments instituted (see Data and Safety Monitoring Plan below).

Suicidality and SSRIs

On September 13-14, 2004, the FDA held hearings to review the safety and efficacy of antidepressant medications in youth, specifically the efficacy of antidepressants in childhood depression and the potential risk for a suicidal ideation and behavior adverse event (suicidality) early in treatment. Although no individual study

had a clear signal and no suicides occurred, the FDA concluded that treatment with antidepressants may be associated with suicidality in some youth. Based on these data, the FDA Advisory Committee (a) recommended a black box warning that documents the risk of suicidality for all antidepressant use in youth; (b) mandates a medication guide for parents with each prescription; and (c) requires closer monitoring of all youth taking antidepressant medication. The FDA visit schedule is congruent with that used in the present study. Although the black box warning may reduce unnecessary prescribing and improve practice standards, it may also result in unanticipated and increased barriers to pharmacological treatment for anxious youth that could otherwise benefit from this form of intervention. In order to precisely estimate the benefit/risk ratio of SSRI use in youth with ASD and clinical anxiety, it will be helpful to identify the specific benefits/risks of sertraline in a large scale clinical trial. It is relevant to note that assessment of adverse events in the present study (like CAMS and TADS) is exceptional in quality relative to industry-standard practice.

Protection Against Risk

Effective screening and psychiatric evaluation will rule out psychiatric conditions that may prevent someone from participating in this study. Once the subject enters the study, an experienced research team will closely follow him or her. The research team has considerable expertise in monitoring the safety of subjects participating in research studies. Drs. Pakyurek, Solomon, and Winder-Patel will be available for research subjects 24 hours a day, 7 days a week. If at any point in the procedures symptoms become distressing or dangerous, subjects will be withdrawn from the study and, if necessary, treatment will be instituted. Adverse effects will be monitored very closely throughout the study, through structured assessments and clinical interactions. The project coordinator and the respective clinician will conduct inquiries regarding any health complaints, recent illness or injury, need for medical consultation since the previous visit. This will ensure that we are detecting and appropriately responding to any adverse event experienced by the child while maintaining the blind of the IE (i.e., asking the child about certain side effects may be suggestive of treatment arm). We will use the same coding system as CAMS for reported complaints: reported complaints will be coded as Mild, Moderate, Severe, Serious, or Fatal (see below for definitions of each).

- Mild: AE poses no interference and no intervention is required
- Moderate: AE poses some interference OR requires some intervention – e.g., lowering the dose of the medication.
- Severe: AE poses some interference AND requires intervention.
    - Serious AEs are defined as follows:
        - Life threatening
        - Potential for permanent disability
        - Requiring hospitalization (or prolonging hospitalization)
        - Intentional Drug overdose
- Fatal AE

When the clinician elicits an adverse event (AE), it will be documented on a case report form, regardless of suspected relationship to the treatment arm. For all AEs, the investigator will obtain sufficient information to determine the onset, course and outcome of the AE. The treating clinician will make a judgment about whether the AE can be attributed to the study treatment. Attribution is classified as:

- Definite: AE is clearly related to study treatment
- Probable: AE is likely to be related to the study treatment
- Possible: AE may be related to study treatment
- Unlikely: AE is doubtfully related to the study treatment
- Unrelated: AE is clearly not related to the study treatment

AE complaints will be relayed to the PI (Dr. Solomon) and psychiatrist (Dr. Pakyurek) who will take appropriate action, which may include monitoring, adjunctive intervention within study protocol, or removal from the study and provision of off-protocol intervention.

The interviews during the course of the study involve no specific risk or discomfort beyond those of a standard clinical interview. All interviews are conducted by experienced clinicians sensitive to the developmental age of the child and experienced in ASD. If necessary or requested by the child or parent, any interview can be interrupted or terminated. The family (parent and patient) are clearly informed that they are free to terminate participation in the protocol at any point.

Prevention of Withdrawal Symptoms

All female subjects who are of childbearing age as assessed by our measure of puberty are required to have a pregnancy test. New pregnancies, although unlikely given the age of subjects, will be tracked during the study via parent disclosure. Pregnancy by itself does not require premature termination, but would be discuss internally with our team to determine what is in the best interests of the patient/family. Although likely infrequent, sexually active girls must agree to use an effective form of birth control, either hormonal (BCP, Depo-Provera or Norplant), spermicide (foam or vaginal suppository) or a barrier method (condoms, diaphragm, cervical cap) or a combination of barrier/spermicide contraception in order to participate in the study.

SSRIs are remarkably free of electrocardiographic impact; hence, there is no requirement for baseline or serial electrocardiographic monitoring. Our procedures for monitoring side effects, as outlined in the study procedures, will reduce the likelihood of adverse reactions. We closely monitor adverse events in all treatment arms and medication-related side effects. In addition to discussion of side effects, parents and subjects are informed about potential interactions between sertraline and other medications, both prescribed by other physicians and those obtained over the counter. Subjects are monitored closely for evidence of therapeutic progress and relapse. Those who become more symptomatic without resolution or who develop exclusionary criteria during the trial (e.g. bipolar disorder, suicide attempt) will be removed from the trial.

This project will be conducted in compliance with research statutes outlined in the Health Insurance Portability and Accountability Act. Confidentiality of participants' research information will be carefully protected by the research team. Research staff will be carefully trained about the importance of confidentiality and, consistent with UC Davis regulations, will be required to sign confidentiality agreements. To the extent permitted by law, no participant information will be given to anyone without a signed release by the child's parents. In addition, all paper-generated data will be stored in locked files in the research laboratories, and all computer-generated data through the customized online database we will use will be maintained in password limited network drive files that are regularly backed-up (see Core D). On any paper forms (other than the consent/assent document), only code numbers will be used on the actual data-gathering tools. Due to the prospective nature of the study, a separate record linking the code numbers to participant identifiers will be kept in a locked file, completely separate from the data. The other procedures to ensure confidentiality follow the regulations and policies of UC Davis Data file archival and back-up will be performed on a regular basis as part of our data management program.

Adverse Event Monitoring and Adjunctive Services and Attrition Prevention (AE/ASAP)

Overview. An adverse event (AE) is defined as any adverse change from the subject's baseline (pretreatment) condition, including any inter-current illness, that occurs during the study, whether considered related to the experimental treatment or not. —Side effects are AEs that are thought by the pharmacotherapist or psychotherapist to be related to the study drug or CBT treatment. Adverse event monitoring is linked to procedures for assessing symptoms (e.g. suicidality) and concomitant medical and mental health treatments. Adverse events may or may not trigger intervention procedures.

Suicidality. In response to the FDA Black Box warning regarding the risk for suicidality events associated with SSRI treatment, study physicians will closely monitor subjects in the medication and placebo groups at each study visit to document any onset or change in suicidal ideation or related behavior and take appropriate action if needed.

Side Effects/Adverse Events. Side effects and adverse events are assessed before each treatment visit for all treatment conditions by the project coordinator. The project coordinator asks the following general question to both the child and parent: —"I want to find out how you have been feeling since your last treatment visit on [DATE]. Have you had any health or other problems since your last visit and today? I'm talking about something that started to become a problem or an old problem that got much worse." The project coordinator records patient or parent responses and gives this form to the treating clinician who reviews the responses to determine severity, causal relationship, action to be taken, and outcome status.

Risks associated with Functional Magnetic Resonance Imaging

All neuroimaging will be carried out in line with standard safety procedures established at the UCD Imaging Research Center, and in accordance with the regulations of the U.C. Davis Institutional Review Board. There are no known side effects of fMRI scans. Participants who have any metallic materials within the body must notify the study team prior to the scan. Metallic chips, materials, surgical clips, or foreign material (artificial joints, metallic bone plates, or prosthetic devises) can significantly distort the images obtained by the fMRI scanner. Participants who have heart pacemakers, metal implants, or metal chips or clips in or around the eyeballs cannot be scanned with an MRI because of the risk that the magnet may move the metal in these areas. Similarly, participants with artificial heart valves, metallic ear implants, bullet fragments, and chemotherapy or insulin pumps should not have MRI scanning. During scanning, the participants are asked to lie in a closed area inside the magnetic tube. Some may experience a claustrophobic sensation during the procedure. Therefore, if participants have any history of claustrophobia, this should be reported to the study team. MRI scanners also make a lot of noise. Sensitivity to sounds also should be discussed with the study team prior to the scan. In the event that subjects become anxious or fatigued during assessments, they will be able to report this to the staff immediately via microphone, and they will be given breaks or may elect to discontinue the scan. Pictures obtained from imaging will not be given routine review by specially trained physicians who interpret MRI scans. However, if in the routine administration of the MRI pictures, the MRI research technicians do notice any possible problems, they will notify the PI who will consult with a member of the UCD Radiology Department. When the radiologist reads the scan, identifying information will be removed to protect confidentiality. If such incidental findings may be significant to the patient, problems will be discussed with participants by Drs. Solomon and the radiologist, who will help them obtain an appropriate referral.

Contraindications and warnings associated with MRI scanning include:

a. Electromagnetically activated implants: The use of the MR system is contraindicated for patients who have electrically, magnetically, or mechanically activated implants (for example, cardiac-pacemakers) because the magnetic and electromagnetic fields produced by the MRI system may interfere with the operation of these devices. Cardiac pacemakers are likely to be susceptible to interference from the magnetic and RF fields produced by the MR system. This interference may destroy or negatively affect operation of these devices. Since interference to cardiac pacemakers in magnetic fields has been observed in as low as 13 gauss field, persons with cardiac pacemakers or other implanted electronic devices are prevented by clearly marked doorways from entering the zone where the magnetic field exceeds 5 gauss.

b. Metal flakes or slivers: Metal flakes or slivers on or inside the patient may be present in eye make-up, tattoos, or as a result of exposure in a metal shop or similar environment. Presence of these materials may result in heating of tissues containing the metal. Precautionary measures include removal of eye makeup, and attentiveness by the subject to increased warmth in the affected tissues. The presence of these materials may preclude scanning, if the Investigator feels that the subject may not be attentive to gradually increased warmth during the scan. A history of long-term exposure to airborne metal flakes is a contraindication to scanning, since metal flakes in the eye that twist as a result of magnetic forces may result in permanent loss of sight.

c. Metal implants/prosthesis: MRI is contraindicated for patients with certain types of metal implants. The magnetic field of the MR system exerts a force on ferromagnetic objects within the field. This force can cause a ferromagnetic implant, such as an aneurysm clip, surgical clip, or prosthesis, to move or be displaced. Also, if the implant is large, currents can be induced in the metal by the magnetic field (eddy currents are induced by the pulsed gradient fields) to cause heating of the implant and possible damage to surrounding tissues. Limb braces, traction mechanisms, stereotactic devices or external prosthetic devices should not be placed in the system. The

RF field is more intense near electrically conductive objects with points or sharp edges as occurs with external prostheses. The intense fields generated can cause electrical discharge and sparks between these prostheses and the patient or RF coils.

d. Pregnancy and infants: The safety of the MR system for imaging fetuses has not been established. Exposure of an unborn child to the strong magnetic field may be harmful. Therefore, parents of participants that are pregnant, or for whom the possibility of pregnancy exists, will be prohibited from entering the 3T MRI suite.

e. Projectile hazard: The magnetic field generated around the magnet of the MR System is strong enough to attract ferromagnetic objects with great force from 10-20 feet away. Near the bore of the magnet, this force can be strong enough to attract objects into the air toward the center of the magnet. Such objects are projectiles that can cause injury or death to subjects being scanned. A Zone of Prohibited Entry is defined around the magnet. Outside of this zone, ferromagnetic objects are not sufficiently attracted by the strong magnetic field to become projectiles. Entry into this zone is limited to a single doorway. The presence of a heavy door, attached Warning signage, and study staff with annual training in MRI projectile safety are present in a 1:1 ratio of research participants (infant, mother, father) minimizes the risk of some person bringing a ferromagnetic object in close proximity to the magnet.

f. Quench Hazard – Asphyxiation Risk: In normal operation, the cryogens used in the magnet of the MR System are recirculated in a closed system. If the magnet quenches (wires lose superconductivity, and magnetic field rapidly drops to zero), the cryogens will boil off at a very high rate. If the ventilation system is not adequate or fails, nitrogen and helium gases fill the room and may cause asphyxiation. At the UC Davis Imaging Center, cryogen gases are vented directly to the outside in accordance with specifications in the Pre-Installation Manual, to eliminate this risk.

g. RF antenna effects: If metal wires or electrodes, such as electrocardiograph (ECG) leads, are attached to the patient being imaged, the RF energy radiated by the imaging coils may induce sufficient electrical currents in the lead wires to cause burns where the electrodes or wires contact the skin. Technicians involved in patient setup and handling have been instructed by UC Davis staff, on the proper setup of the electrodes and leads to eliminate this risk.

h. Clinical Hazards: The confining conditions of the MR system can precipitate claustrophobia (fear or anxiety while in closed or confined spaces) in a patient, and in some instances claustrophobia will preclude scanning. Many MRI pulse sequences produce a loud (90-110 dB) jack-hammer sound that can cause hearing discomfort and eventual damage if the appropriate hearing protection is not used. The subjects will be fitted with disposable earplugs and/or sound attenuating headphones to reduce this sound to an acceptable level.

i. Access to MR area: Access to all areas exceeding the 5 gauss level will be controlled by doors, warning signs, barriers, staffed entry locations, and or vigilance by the MR system operator (Technologist) to assure avoidance of incidents. Access to the magnet room by any personnel will be closely controlled for the safety of all persons and equipment.

j. Biomagnetic Hazards: It is uncertain whether subtle genetic or molecular changes could be caused by the magnetic fields produced by the MR System. To date, no harmful biological effects have been demonstrated at the magnetic field strengths (1.5T) and exposure times (90 minutes maximum) utilized by the MR System. At the present time, the likelihood of any significant biomagnetic effect is considered to be very low. As part of normal documentation, adverse effects felt by the subject during the scan will documented for review and follow-up. Blood draws are minimally invasive and pose low risk. There may be some discomfort, minor bruising or swelling associated with taking the blood sample. Sterile procedures will be followed but there is a very small chance of infection at the site where blood is taken.

Minimizing anxiety produced by scanning

We currently have a mock scanner environment that is able to fully simulate the experience of an MRI study in our 3T scanners. This practice can reduce anxiety during actual scanning. In the mock scanner we have a

complete audio and video system, as well as a stimulus response system. As a result, participants can experience a faithful replication of both structural and functional imaging studies complete with the exact sequence sounds that they will hear. During actual scans, participants can interact with the experimenter in the auditory and verbal modalities via headphones and a microphone, and in the visual modality via a webcam mounted at the experimenter's workstation. In this way, whenever the participant is not practicing a task for functional imaging or watching a movie as they would during structural imaging, they can see, hear and interact with the experimenter at all times. All subjects who become fatigued will be given breaks and snacks as needed. They may also elect to discontinue the scan at any time. Special efforts will be made to ensure that participation is a good experience for subjects. In the current scanning protocol, we will work with individuals who are children and who may have ID. While some of these individuals are very capable of completing fMRI tasks with limited practice, we recognize that many will need more extensive training. For our study, we have developed a method for preparing children for the IEP task. We use visual materials that show the participants what to expect during the sessions with us that will be composed of small chunks of practice, calibration, and scanning with reinforcements given after successful completion of each chunk. We let them play games on the Computer (practice the task outside the scanner environment), practice both this same game and calibration of the eyetracker and receive a reward (e.g., toys or snacks) their choice (play 2 games in pretend scanner), lay in real scanner where the eye tracking calibration will be completed (Lay in MRI Scanner), and finally do the task in the scanner and receive another reward.

Protections Against Risk

The MIND Institute clinic has been designed with the needs of children with neurodevelopmental disorders in mind, and therefore the stresses of an evaluation in a new environment will be minimized. Only highly experienced staff will work directly with the children and their families. In order to minimize the stress to parents of answering questions including those about family mental disorders, they will be assured that their child's access to medical or social services will not be affected by the decision to participate or not, that they are under no obligation to answer all questions, and that they have the right to refuse to participate in any aspect of the study or to withdraw from the study at any time. The risk of a loss of confidentiality is minimized by the training of our staff and the high level of security in our information systems. Other identifying information, such as name, social security number, etc., will not be accessible to anyone outside the study staff, and only to those study personnel who have a need for such information. The databases used for tracking our contacts with subjects are stored on different servers from the ones containing analytic databases. No analytic databases will contain any identifying information besides dates and spatial coordinates of residences needed for the analyses. The code linking ID numbers to other personal identifying information will be kept in a locked file cabinet, and in electronic files that do not contain any other information and do not exist on computers containing any other information about the participants. The APP has secured a Certificate of Confidentiality from the United States Department of Health and Human Services to further protect disclosure of our research participant data from subpoena or court order.

Potential Benefits to Subjects

There are several potential benefits to participation in this study: having comprehensive psychiatric and medical assessments and carefully-monitored, state of the art treatment, and no burden of financial cost. In addition, there is a likelihood that the patient's anxiety symptoms will improve with active study treatments, and as a consequence the subject may experience improvement in their academic, social, and family functioning. Written reports of the results of participants' performance on all standardized developmental, diagnostic, and behavioral procedures used in the study will be available. Copies of structural scans also will be given to subjects upon request.

Multi-Site Collaboration

The study will be conducted within the UC Davis system at the sites of the MIND Institute and the Imaging Research Center. We will collaborate with Dr. Jeff Wood from UCLA, who will train our staff in the BIACA therapy program.

Community-Based Participator Research & Sharing of Results with Subjects

The goal of autism research is to help people with autism spectrum disorder (ASD) by increasing understanding of their difficulties and learning how to minimize their challenges and maximize the quality of their lives. It is not enough to address and answer fundamental questions with well-designed experiments conducted by expert scientists. If the findings are not made widely available to practitioners and those who have the most to gain from them – persons with ASD and their families and caregivers – then a key aim of the research is not realized. To insure that this perspective is ever-present in the activities of the Center, the Dissemination and Outreach Core (DOC) has been developed and aims to (1) widely disseminate the findings of the Center for the Development of Phenotype-Based Treatments of Autism Spectrum Disorder to practitioners as well as persons with ASD and their families and caregivers; and (2) support two-way communication between the scientists of the Autism Center of Excellence and the broad ASD scientific community, along with the community of stakeholders and practitioners both locally and nationally. Our project will collaborate with the DOC to share findings and research information with families.

The Center plans to meet these goals through the following strategies:

- Provide semi-annual live interactive webinars on topics ascertained by needs assessment for audience of families, students, and researchers
- Provide MIND/CEDD Summer Institute panel annually on ACE related topics**.**
- Discuss project-related topics with stakeholder audiences at lay oriented MIND Institute lecture series such Minds behind the MIND http://www.ucdmc.ucdavis.edu/mindinstitute/events/mindsbehindmind.html
- Develop Center website to include project overviews, team bios, calendar of events, links to resources, tutorials in a variety of media formats, fact sheets, and to allow for suggestions, input, feedback through a two-way communication system on the MIND Institute website
- Create and maintain project Facebook, Twitter and similar social media accounts to post events, research findings, increase outreach and increase communication with stakeholders
- Attend and provide brief project overviews and two-way discussions at all ASD support groups in the population centers surrounding the MIND Institute, including the Association for Adults with Developmental Disabilities (*AADDPA)*, *Vamos a platicar (Let's Talk)* and Families for Early Autism Treatment (FEAT)
- Invite one Distinguished Lecturer (from the monthly MIND Institute lecture series which is open to the public) each year whose expertise lies in phenotype-treatment interactions and whose topics and styles are equally fitted to family and scientific stakeholders. Scientists who are also family members of a person with ASD will be prioritized
- Provide two-way communication between the investigators and stakeholders (including practitioners) through focus group activities and through needs assessment of stakeholder groups in Year 1, formation of community advisory groups of family/self-advocate stakeholders and practitioners in Year 1, and organize discussion meetings with those groups annually in subsequent years.
- Maintain regular contact with participants and families including:
    - A quarterly newsletter to distribute to families that highlights study results progress, provides clarification regarding general questions that families may have, and MIND Institute event information.
    - Parent education meetings held annually to inform parents of study findings and answer any questions.

Provisions to Protect the Privacy Interests of Subjects

The research team will carefully protect confidentiality of participants' research information. Researchers will be carefully trained about the importance of confidentiality and will be required to undergo HIPAA training. In addition, all paper generated data will be stored in double-locked files at MIND Institute; and all computer-generated data within our customized online database management program will be maintained in password-limited network drive files. Participant names (or any other identifying information) will not be kept on study documents themselves. Instead, code numbers will be used on any actual data-gathering tools, both within the online database management program and for any paper documents. A separate record linking the code numbers to the participant identifiers will be kept in locked files, completely separate from the data.

Compensation and Reimbursement

Research participants will be compensated at $100 per visit/day of testing for the screening visit 1 (up to $300), visit 17 ($100), and visit 19 ($100) up to a maximum of $500 per subject for study participation during Phase 1. If families request to split a visit into multiple parts to accommodate schedule, they will not receive extra compensation for the additional visit. This compensation includes the amounts used as incentives for the fMRI task mentioned above. Compensation will be provided in the form of a visa gift card or electronic gift card to Amazon or Target based on the participant's preference.

Travel reimbursement will be offered to participants for whom traveling to the MIND Institute for study visits poses a financial burden affecting their ability to participate in the study. The financial impact of study participation will be discussed during the phone screen and families will be offered travel reimbursement if appropriate in the form of a visa gift card. Participants traveling 25 miles or less round trip to the MIND institute or laboratory testing location will be provided with $25 per visit and those above 25 miles roundtrip will be provided with $50 per visit. Travel reimbursement maximum will be $50 per visit due to the anticipated local recruitment area due to the frequency of study visits.

Research participants taking part in the training (consented under the training ICF) will be compensated $50 per visit per day.

There will be no charge to the subject or their family for participating in this study. Neither the subject/family nor their insurance carrier will be charged for taking part in this research.

Drugs

This study will use sertraline HCl (12.5-125mg/day) or placebo, as outlined above. The drug or placebo will be given in capsule form. Commercially available sertraline tablets will be purchased. Matching placebo capsules will be compounded by the UCD Investigational Drug Service (IDS) by over-encapsulation.

☒We confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be handled only by authorized investigators or designated study staff.

☒ We confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators or designated study staff.

ClinicalTrials.gov Registration

This project will be registered and details will be included in the language of the informed consent form for this project.

Statistical Analysis Plan

Numerical and graphical descriptive statistics will be used to summarize the data on all randomized participants and to confirm the absence of group 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 PARS 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 all arms simultaneously, employing general linear mixed models (GLMMs)(112) with treatment group (*BIACA, sertraline, pill placebo*) and time (Screening, Post-Treatment) 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. (113, 114) This will allow us to use all available data from all subjects in an intention-to-treat (ITT) framework. We are able to control for potential confounding variables in terms of their impact on group differences and changes over time. All tests will be reported using two-tailed family-wise significance level α=.05, using the Holm-Bonferroni correction.(115) To model anxiety symptoms, we will use the PARS as the dependent measures in a mixed effects regression with treatment group as the between-subject factor, time (Screening, Post-Treatment) as the within-subject factor and a group x time interaction, with the latter used as evidence for differential rates of change. Power Analysis: We will enroll a total of N=132 subjects for the RCT, randomizing 44 to each treatment arm. This sample size was chosen to provide the optimal balance between feasibility of recruitment and maximization of power for the aims outlined above. 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 (81) Under these assumptions, using GLMM we have 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=.54 at Post-Treatment. Maintenance will be analyzed from post-treatment to follow-up for treatment responders in each condition.

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