Protocol

Care Improving Cognition for ADolescents on the Autism Spectrum (CICADAS)

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INVESTIGATOR

NAME:_____ Signature:_____

DATE:

By signing here, the investigator acknowledges that he or she has reviewed and understands the protocol referenced above and agrees to comply with it. Additionally, the Principal Investigator's signature indicates that his/her site has not been the recipient of prior FDA 483 reports or other detailed audit findings. Any and all prior FDA 483 reports or regulatory warnings have been submitted to Posit Science Corporation prior to the commencement of this clinical trial.

Title

Care Improving Cognition for ADolescents on the Autism Spectrum (CICADAS)

Principal Investigator and Key Staff

The trial is sponsored by Posit Science Corporation (PSC) and is funded exclusively by the National Institutes of Health (NIH). Posit Science will serve as the coordinating and data monitoring and management center for this study. Key staff and site information may be found below:

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Site Investigator and Study Location

The University of Minnesota Departments of Psychiatry & Behavioral Sciences and Pediatrics will serve as the primary recruitment sites for this study. The Site Principal Investigator, listed below, will oversee participant recruitment and enrollment for this clinical trial.

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Overview

This is a validation study to evaluate the acceptability, feasibility and impact of CICADAS (Care Improving Cognition for ADolescents on the Autism Spectrum), a clinician-assisted, digital application that aims to prime the brain to engage in flexible, adaptive long-term learning about social-emotional events through closed-loop technology. The goal of this study is to evaluate the CICADAS app in adolescents with Autism Spectrum Disorder (ASD) and to prepare for a large-scale efficacy trial in this population.

Specific Aims

This study will employ an innovative and evidence-based digital intervention that includes ten digital assessments (CICADAS app) that will capture data on sensory processing abnormalities and associated cognitive deficits. We will leverage pilot data collected in adolescents with Autism Spectrum Disorder (ASD) and accumulate preliminary evidence for CICADAS app to function as 1) a stand-alone treatment; 2) a primer for PEERS (Program for the Education and Enrichment of Relationship Skills); 3) an enhancer for PEERS. This study will test CICADAS app in adolescents with ASD in a three-arm, active-controlled, randomized crossover trial to document the acceptability and evaluate its potential as a stand-alone treatment, as a primer for PEERS, or as a treatment enhancer of PEERS.

Background

Adolescence is a period of heightened, socio-affective, experience-dependent learning and neural plasticity,[16,17] which manifests as increased regulation of emotional reactivity and greater social understanding—functions that are necessary to navigate a complex social world.[18] During this period, neural networks underpinning affective information processing functionally mature,[19,20] leading to adaptive changes in how adolescents experience and regulate emotions in response to social cues as well as how they understand the social world and others' mental states.[21] However, for vulnerable populations, including adolescents with Autism Spectrum Disorder (ASD), exposure to complex interpersonal situations and peer networks can be challenging, and the avoidance of social interactions may preclude meaningful social experiences and impede social skills development.[22]

The cognitive-behavioral therapy (CBT) based PEERS (Program for the Education and Enrichment of Relationship Skills) is one of few evidence-based treatments available that target social skills in adolescents with ASD. PEERS is a parent/caregiver-assisted, 16-week social skills intervention with 500+ certified providers across 70 countries and multiple Randomized Controlled Trials (RCTs) demonstrating its efficacy and effectiveness for adolescents.[25,26] The program teaches how to solve real-life social dilemmas, appraise affect and social contexts, and initiate and maintain conversations while receiving feedback from peers

and clinicians. Additionally, structured practice interactions during socialization activities (e.g., playing sports, games, etc.) are integrated into the curricula. Concurrently, parents attend separate sessions and are taught to assist their teens by providing appropriate feedback as participants work on forming and maintaining friendships via weekly homework assignments. Notably, some adolescents benefit from PEERS more than others, implicating individual differences in response to treatment and highlighting the potential for developing treatment enhancers.[27,28]

While myriad approaches have been attempted to remediate social functioning deficits in ASD, few have considered how sensory processing is a prerequisite for intervention success. Although Sensory Processing Abnormalities (SPA) have been noted since the earliest reports of ASD,[1] historically, they had been considered secondary consequences of social cognitive processing impairments. Only in the most recent revision of the DSM[2] was "hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment" added to the diagnostic checklist for ASD. However, recent estimates of sensory symptom prevalence in persons with ASD range from 69% to as high as 93%.[3] Sensory processing difficulties correlate highly with levels of autistic traits in the general population, implicating SPA in social interaction difficulties.[4] Further, prospective studies suggest that sensory difficulties might even precede and predict difficulties in social functioning.[5,6] Sensory processing is crucial in the forming of reliable environmental percepts; perturbations in this process can have broad implications across different levels of cognitive functioning, impacting adaptive functioning across the lifespan. These sensory symptoms may originate from differences in low-level processing in sensory-dedicated regions in the brain, offering insight into circuit-level alterations in ASD. In fact, SPA are hypothesized to be an etiological and maintaining factor of social cognitive deficits in ASD, and are strongly associated with impaired community functioning, reduced capabilities for independent living, and reduced quality of life.[29] These challenges in processing and integrating the elements of the dynamic social information into a stable representation are considered the underpinnings of social cognitive impairments,[15] and might render the acquisition of social skills more problematic in ASD individuals with SPA[30]. Thus, targeting SPA to enhance social skills intervention is warranted.[31,32]

Although PEERS teaches adolescents to consciously alter their attention and behavior through instruction and practice, the program is unable to systematically target SPA and strengthen processing of basic sensory information. One promising approach to mitigate SPA may be through computerized Social Cognitive Training (SCT), which leverages repetitive implicit learning mechanisms to promote more adaptive processing styles for affective stimuli.[11] One well-designed RCT has tested the combination of SCT and social skills training in adults with ASD and reported gains in cognitive abilities and functional outcomes.[32] However, no studies

to date have investigated whether SCT can enhance response to social skills interventions in adolescents with ASD.

In recent years, multiple computerized SCT programs have been developed with the goal of improving social cognition in individuals with ASD (see *Table 1 for trials that included adolescents*). While data show promise overall, 30% of the participants did not show gains in social cognition beyond expected practice effects.[33–35] In addition, some investigations in ASD reported improvement on the SCT exercises but no transfer of these gains to untrained cognitive outcome measures.[9,36] Further, methodologies across SCT trials have been inconsistent—e.g., small sample sizes, single-arm or non-randomized controlled (NRS) designs, non-validated measures, lack of follow-up assessments, and permissive procedures. To address these limitations, we have integrated our team's combined expertise in clinical care of youth with ASD, developmental neuroscience, and our considerable track-record in the development of digital platforms that provide assessment and treatment tools based on the principles of neuroplasticity,[10,37,38] to identify three potential areas of innovation for SCT in ASD:

1) Existing SCT for adolescents with ASD target sensory processing using fixed repetitive parameters. This approach does not capitalize on the neuroplastic potential of circuits underlying information processing, and does not take advantage of the unique sensitive period of brain development that occurs in adolescence to maximally promote adaptive learning.[16,19] Over the past three decades, research has documented the remodeling of distributed cortical and sub-cortical responses as an individual acquires new perceptual, cognitive, motor, or executive control abilities.[39–42] This training induces selective positive physical changes in synaptic numbers and strengths that result in the "specialization" of neuronal patterns that support emergent behaviors.[39] This synaptic-plasticity-generated specialization of cortical and sub-cortical networks represents the neural substrate of new training-induced learning. Neuroplasticity-based SCT (NB-SCT) is designed to drive stimulus-specific cell assemblies to represent all parametric aspects of behaviorally relevant inputs or actions in increasingly robust, discriminative, and more-salient forms. For example, a rich body of work has shown neuroplasticity-driven behavioral changes leading to gains in cognitive operations including: perceptual abilities;[43–45] cortical sampling rates and integration times;[46,47] processing speed;[48,49] representations of the spatiotemporal and spectrotemporal features of complex acoustic, visual, and tactile stimuli.[48,50–52] Additionally, a small number of neuroimaging studies have examined neural effects of SCT interventions in ASD and have reported neuroplasticity that results in activity/functional connectivity more similar to that of typically developing controls.[8,53] For example, Bolte and colleagues[9] demonstrated that facial affect recognition training in youth with ASD led to an increase in amygdala and fusiform gyrus activation post-training that correlated with cognitive improvements. Hence, we designed a suite of training exercises (see *Innovation*) that targets ASD-related SPA.

2) Existing SCT for ASD is non-personalized and does not take into account cognitive endophenotypes. Prior trials of computerized cognitive training in ASD have been implemented without knowledge of individual variation in brain function domains that may influence therapeutic response[54,55]. This "one-size-fits-all" approach to SCT is problematic, as treatment failure occurs often which incurs substantial cost to the patient, family, and social system. To bend the curve on the individual outcomes of ASD and maximize response to SCT, it is necessary to characterize sensory processing in each individual participant and use this information to set targets and tailor the exercises accordingly. Thanks to data collected from 200+ adolescents without psychiatric illnesses, we can rely on brief assessments (*see Innovation*) that identify and monitor SPA at a subject-specific level, and propose personalized training exercises that target individual needs.

3) SCT is only available in specialized treatment centers. SCT programs often have a high scheduling burden, requiring multiple weeks of participation and regular in-person clinic visits. This time commitment can be untenable for caregivers who are employed, have other responsibilities to manage, or are without transportation. Additionally, for those who do seek treatment, barriers to receiving it include geographic location, availability of trained therapists, long waiting lists, and the requirement to take time off from school for clinic visits.[56] The remote delivery of SCT through digital devices enables scheduling flexibility and decreases time burden, thus improving accessibility and compliance with intervention requirements, resulting in an increase in cost-effectiveness.[57] In short, digital technology can facilitate access to, and engagement with SCT. In an effort to address these issues and improve outcomes, we propose CICADAS (Care Improving Cognition for ADolescents on the Autism Spectrum)—a digital application that provides an assessment of SPA to tailor the delivery of adaptive, individualized NB-SCT exercises for ASD. By systematically targeting SPA and social cognition deficits, CICADAS app is designed to prime the brain to learn cognitive and relational strategies taught during PEERS groups. We hypothesize that the delivery of the CICADAS app will maximize the impact of PEERS, promoting the generalization of learned skills in the natural environment, and ultimately improving real-world social functioning.

Pilot Trial Design and Procedures

Participants will be recruited to join a pilot trial prior to the implementation of the three-arm, randomized crossover trial to assess feasibility and initial efficacy of CICADAS app in adolescents with ASD. During the pilot trial, three focus groups will be organized with a group of three adolescents with ASD and two PEERS clinicians to refine CICADAS app, qualitatively evaluate its manageability, clinical usefulness and acceptability, and ensure that the user experience and interface are sufficiently engaging to motivate sustained program use. After the focus groups are completed, participants will be granted access to CICADAS app for two weeks to test its features and evaluate its usability. At the end of the 2-week trial period, participants will offer feedback on the app through a 1:1 user interview with a member of the

research team. It is expected that participants will be enrolled in the pilot trial for approximately 4 weeks.

Participants must be between the age of 11 to 18 (inclusive) and have a clinical diagnosis of ASD. Participants must have access to reliable Internet connection and must be willing to engage in remote and/or in-person activities to qualify for enrollment.

Prior to initiating any pilot trial procedures, study personnel will screen potential participants (either over the phone or in-person) using an IRB-approved screening questionnaire that assesses for inclusion and exclusion criteria. If the potential participant appears eligible, they and their parents/legal guardian(s), when appropriate, will be invited to a consent/assent discussion with a designated team member prior to enrollment. Consenting/assenting to research activities will take place remotely or in a private room at the study site. During the consent/assent discussion, the qualified site study personnel authorized by the Site Principal Investigator (Site PI) and the potential participant and their parent/legal guardian will discuss the nature, purpose, and procedures of the pilot trial, the possible risks and benefits of participation, confidentiality, and the voluntary nature of participation in the pilot trial (emphasizing the participant's right to withdraw from the focus group at any time). Participants will also be informed of the compensation procedures; specifically, participants will be paid $10 for completing the consent and screening procedures, $25 for participating in each focus group session, $25 for completing 2-weeks of CICADAS app activities, and $15 for completing a 1:1 user interview. Participants that complete all activities will earn a total of $125. Compensation will be provided through CashPass, a reloadable debit card through a third-party vendor, CT Payer. Payment will be provided upon exiting from the pilot trial, following the completion of the 1:1 user interview. If a participant leaves early, for any reason, and does not complete all focus group activities, they will be paid only for activities they have completed. After potential participants have agreed to participate in the pilot trial and completed informed consent/assent procedures, study personnel will confirm eligibility via clinical/medical history and assessments as needed.

Once three participants are deemed eligible and enrolled in the pilot trial, they will be scheduled for three focus group sessions that could occur in-person or remotely, to be completed over the course of approximately 2-weeks. Each session will last approximately 1 hour and will be facilitated by PEERS clinicians. After feedback from the focus group sessions is implemented into the app and dashboard design, the three adolescents will be granted access to the CICADAS app and engage in a 2-week trial period. This trial period will ensure that CICADAS app assessment data adequately orient the delivery of individualized neuroplasticity-based social cognitive training (NB-SCT) exercises. At the end of the 2-week trial period of CICADAS app, participants will be asked to rate their enjoyment, ease of use,

product quality, and perceived usefulness in a 1:1 user interview. Finally, we will submit these data from the trial period to our consultant to confirm that CICADAS app is suitable for the feasibility trial.

General Study Design

We will employ a three-arm, active-controlled, randomized crossover trial to assess the safety and efficacy of CICADAS app in adolescents with ASD, and to evaluate its potential as a stand-alone treatment, as a primer for PEERS, or as a treatment enhancer of PEERS. We will randomize adolescents with ASD (ages 11-18) to CICADAS only, PEERS + CICADAS app, or PEERS + Active Control app.

Approximately 56 participants will be consented to ensure the successful completion of 48 participants (16 participants per treatment arm). A diagnostic interview will be performed to determine eligibility. Following inclusion and enrollment, participants will complete a set of assessments prior to the intervention to establish their baseline performance. Participants will then be randomized to the CICADAS only group (Arm A), PEERS + CICADAS app group (Arm B), or PEERS + Active Control app group (Arm C) and spend up to 16 weeks engaged in their assigned intervention. After 16 weeks, a full battery of assessments will be administered. For the next 16 weeks, Arm A will continue with PEERS only and Arms B and C will receive no treatment during this period. At the end of the intervention period, a full battery of assessments will be administered a second time to evaluate changes in performance. Finally, participants will be asked to fill out an online exit survey to rate enjoyment, usability, perceived benefits, and ease of fit into schedule.

During the first intervention period, participants assigned to the CICADAS only will complete NB-SCT exercises for 16 weeks. Participants assigned to PEERS + CICADAS will engage with the CICADAS app and complete weekly 1-hour PEERS group sessions for 16 weeks. Participants assigned to receive the PEERS + Active Control will engage in the Active Control app and complete weekly 1-hour PEERS group sessions for 16 weeks. During the second intervention period, participants assigned to receive PEERS only will complete weekly 1-hour PEERS group sessions for 16 weeks. During both intervention periods, these participants may have weekly electronic check-ins with site study personnel (as needed). The CICADAS app and the Active Control app icons, design and user experience will look the same as to not unblind the participants.

Each PEERS group session will consist of a minimum cohort of 3 participants and will meet as a group during the 16 week period. The PEERS clinician will meet with each participant individually for a brief introduction and orientation. The PEERS group sessions will be made available to meet in person or remotely. For remote PEERS group sessions, the study

coordinator and/or PEERS Clinician will create a virtual room open only to cohort participants, explain their role, and make introductions. Next, the PEERS clinician will invite participants to attend weekly 1-hour PEERS group sessions.

The protocol will be conducted in accordance with the protocol submitted to and approved by the reviewing Institutional Review Board and approval will be obtained prior to implementation.

Study Population

The study population comprises adolescents diagnosed with ASD. The study is open to all races, ethnicities, and genders.

Inclusion/Exclusion Criteria

Following informed consent, participants will be screened for the following inclusion/exclusion criteria.

Inclusion Criteria

1) Potential participant is between the age of 11 and 18 (inclusive) at the time of consent
2) Potential participant has a clinical diagnosis of Autism Spectrum Disorder (ASD), as confirmed by medical/clinical records or standardized assessments/interviews (e.g., Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) or Autism Diagnostic Interview – Revised (ADI-R)).
3) Potential participant has an IQ > 70 on the Wechsler Abbreviated Scale of Intelligence (WASI-II) or a comparable measure in medical/clinical records.
4) Potential participant has normal or corrected to normal vision (20/20 or better; self/parent-reported)
5) Potential participant has normal hearing (self/parent-reported)
6) Potential participant is a fluent English speaker, based on participant and/or parent/legal guardian self-report and as determined by the screening clinician, to ensure reasonable neuropsychological results on key assessments
7) Potential participant has adequate sensorimotor capacity to perform the intervention and study activities, including visual capacity adequate to read from a digital device at a normal viewing distance, auditory capacity adequate to understand normal speech, and motor capacity adequate to control and use a digital device, based on participant and/or parent/legal guardian self-report and as determined by the screening clinician and/or study team
8) Potential participant must be clinically stable as a result of therapy or medication regimen for 4 weeks prior to enrolling into the study.
9) Potential participant has reliable access to the internet

Exclusion criteria:

1) Potential participant has history of psychotic disorder(s) and/or seizure disorder and/or seizure episodes within the last 2 years
2) Potential participant has a motor/perceptual handicap that precludes digital device use, as determined by the screening clinician and/or study team
3) Potential participant has problems in performing assessments or comprehending or following spoken instructions, as determined by the screening clinician and/or study team
4) Potential participant has medical illnesses/genetic syndromes deemed to interfere with participation in study activities and/or unstable and/or untreated conditions that may affect cognition, including substance abuse/dependence disorders, ongoing chemotherapy or other cancer treatment
5) Potential participant has a history of head trauma, traumatic brain injury, or other neurological disorder that impairs cognition
6) Potential adult participant scores less than a 14 (75%) on the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). Please note, this criteria applies only to adult participants, age 18, at the time of screening.

Recruitment

Study participants will be recruited through several recruitment mechanisms in an effort to examine engagement and acceptability in a representative sample of adolescents diagnosed with ASD. Following IRB approval, information about the study aims and procedures may be posted on Facebook, Craigslist, Reddit, Twitter, Instagram, Tik Tok, newsletters, the study website, as well as other web-based recruitment sites; in addition, efforts will be made to recruit participants through several community and primary care clinics and/or referrals, school-based settings and/or referrals, community organizations, and publicly hosted information sessions and webinars. Following IRB approval, a CICADAS recruitment video, which includes a brief description of the study and may include members of the study team, may be shared with potential participants, with identified recruitment sources, and the community for recruitment purposes and engagement.

Participants will be recruited through active PEER groups in Minneapolis/Saint Paul and surrounding regions. When patients and families sign up to access PEERS groups, the referring clinicians will conduct a preliminary screen to assess if potential participants may be eligible for the study and encourage them to contact UMN Clinical Research Advocate who will describe research opportunities and, if eligible, put them in contact with the UMN study team. Patients may also contact the UMN study team directly via the phone or the internet (email, website, social media, etc.). Finally, recruitment may extend to online web-based recruitment methods.

The Site study team may host various information sessions and/or webinars within the Minnesota community in an effort to recruit participants. The Site Study team may also contact schools and school personnel (e.g., teachers, nurses, counselors, etc.) and/or school-related organizations within Minnesota to host a webinar or information session about the CICADAS Study. These sessions may include discussions regarding approaches to identify students who may be diagnosed with Autism Spectrum Disorder (ASD). The Site Study team may provide the school staff with resources to refer students of concern (e.g., flyers and other recruitment materials).

As the Sponsor, Posit Science will serve strictly as a coordinating and data monitoring and management site. The Posit Science study team will manage this study using standard and established methods. Site Study personnel will be invited to complete virtual training sessions conducted by the Posit Science study team and/or the PI will visit the Study Site to engage in a hands-on orientation of the digital application and clinician's portal.

Enrollment and assessments will be performed by authorized site study personnel remotely and/or at the study site, the University of Minnesota. Participants will perform the intervention activities remotely in their place of residence or in-person. This project will employ established Sponsor- and Site-procedures for compliance, treatment delivery and communication to ensure standardization of all study procedures.

The emphasis of the benefit will be on advancing science to assist others with ASD. Compensation will be described in appropriate terms that are not overemphasized relative to the remainder of the text. No indication of "free medical treatment" will be communicated. All materials used for advertising or recruitment will have received IRB approval prior to implementation. The site study personnel will manage these efforts and contact individuals that express interest. The aim of this discussion is to describe the study, answer any questions, and if the potential participant agrees, conduct a preliminary screening. Site study personnel will conduct an interview with a screening questionnaire, over the phone or in person, in which potential participants will be asked about the presence of inclusion and exclusion criteria. If the participant appears eligible, they and their parents/legal guardians, when appropriate, will be invited to a consent discussion.

All study team members are required to follow Good Clinical Practices and institutional best practices in the identification and recruitment of research participants. Volunteer selection will be equitable: all participants meeting Inclusion/Exclusion criteria will be offered the opportunity to participate in this study regardless of gender, race and/or ethnic origin. Basic demographic data will be collected from participants screened for participation but not

meeting study eligibility requirements to ensure that the opportunity to participate in this research study has been extended to all potential participants in an equitable manner.

Description of Informed Consent Process

For participants that move forward following the initial screening, every effort will be made to send a copy of the consent form and HIPAA waiver via email ahead of their scheduled appointment. Assent/Consent forms for adults, minors (youth), and parents/legal guardians of minors will be written using appropriate vocabulary and language and will be accessible (non-technical). As minors cannot give legal consent to participate in research, a parent or legal guardian must sign a consent form on their behalf. However, we will still obtain the minor's written or electronic assent to ensure their voluntary participation in the research study. As with consent, the research study will be explained to them in language they will understand.

To ensure that the potential adult participants have the capacity to provide informed consent, a modified version of the UCSD Brief Assessment of Capacity to Consent (UBACC) will be administered. In the modified version of the UBACC, Question 10 was not included as the risk of hospitalization due to research is unlikely, and there is no corresponding information in the consent document. If the participant scores less than a 14 (75%) on the UBACC, the study staff obtaining consent may review the study details and re-administer the UBACC. If the participant is still unable to pass during the second administration, they will not be offered participation at this time. Participants may return for a consent visit in the future if, in the opinion of the clinical care provider and/or the PI, their status has improved and they may have regained capacity to consent to research. In addition, if at any point during the study the staff has reason to suspect that the individual's capacity to provide consent has diminished (e.g., the participant has increased symptoms), the study staff may choose to conduct another consent discussion and/or re-administer the UBACC to confirm that the participant has capacity to provide ongoing consent. If the participant does not show capacity to consent, the PI will review their case and determine whether it would be best to withdraw the participant from the study or place their participation on a temporary hold until the participant is capable of providing informed consent. If the participant is placed on hold, they must successfully complete the UBACC prior to continuing with study procedures.

Potential participants will meet with the designated study team member for assent/consent (paper or electronic) and potential enrollment. Informed consent procedures will occur in-person in a private room at the study site or remotely via phone and/or video call (e.g., Zoom). During this visit, the qualified site study personnel authorized by the PI and the potential participant and their parent/legal guardian will discuss the nature of the trial, the purpose of the research, the trial procedures, the possible risks and benefits of participation, confidentiality and the voluntary nature of participation in the trial (emphasizing the

participant's right to withdraw from the study at any time). Site study personnel obtaining consent will emphasize that the study will not influence that participant's clinical care or their relationship to Posit Science.

Following this discussion, potential participants and their parents/legal guardians will be offered the opportunity and encouraged to ask any study-related questions and enroll by providing written assent/consent on the IRB-approved form. For remote consent discussions, participants and/or their parent/legal guardian will navigate to the electronic consent/assent form shared through REDCap. The electronic consent/assent form has been designed so that the participant and their parent/legal guardian are unable to complete the consenting process without completing the consenting process with a member of the research team. Participants and/or their parent/legal guardian will first receive a "Read Only" version of the consent. Only after the research coordinator has completed the informed consent discussion and determined that the parent/legal guardian and/or participant fully understand all procedures and are capable of informed consent will he/she deliver an "editable" version of the electronic consent form which the participants and/or their parent/legal guardian will be able to sign using a mouse, trackpad, or tablet. For the electronic consent process to be considered complete, the consenting team member will access REDCap in real-time to confirm the parent/legal guardian and/or participant have signed the consent/assent form correctly.

Participants will be allowed as much time as needed, with site study personnel or in private, to review the HIPAA waiver and consent documents before making the decision to participate. Potential participants may invite a friend or family member to be present during the visit, to further discuss their decision to enroll and/or contact (e.g., phone call) a friend or family member that is not physically present for discussion before deciding to enroll. At the potential participant's request, site study personnel may be asked to 'step-out' of the room or end/mute the call during remote discussions, to provide privacy for such discussions. In addition, potential participants will be provided the option to defer their decision to allow them to review the consent form and other study information forms at their convenience, and later reconnect with the study team remotely or return to the site to enroll (i.e., complete the informed consent procedures). No study activities will take place prior to completion of the consenting process.

Participants will not be invited for consent discussions during periods of greater impairment. If a participant is hospitalized for psychiatric reasons during the study, they will be withdrawn from study activities. Additionally, consent to continue in the study will be addressed as needed throughout the study and the participant will be reminded that their participation in this study is completely voluntary and they do not have to continue unless they choose to.

The consenting study team member will inform participants about compensation for their participation in the study. Specifically, participants will be compensated $20 for completing the *Consent and Screening* assessment visit (V0), $20 for completing the *Baseline* (pre-intervention) assessment visit (V1), $20 the *Mid-Intervention* assessment visit (V3), $20 for completing the *End of Study* (post-intervention) assessment visit (V4), and $2 for each 20% of digital app sessions completed up to $10 a week, CICADAS or Active Control apps, during the intervention period (for a total of $160 for 16 weeks). Participants that complete the study in its entirety will earn $240. Compensation will be provided through CashPass, a reloadable debit card through a third-party vendor, CT Payer. For remote assessments, the CashPass card will be mailed to participants to a mailing address of their choice after the completion of the Consent and Screening Visit (V0). In the unlikely event that a participant must repeat an assessment visit due to administrative assessment or site study personnel errors, participants may be provided additional compensation for that session. Compensation during the intervention periods will occur on a weekly basis.

Compensation Schedule for All Participants	
Visit	Compensation
Consent/Screening (V0)	$20
Baseline (V1)	$20
Digital App Sessions ($2 for each 20% of digital app sessions completed, up to $10 a week for 16 weeks)	$160
Mid-Intervention (V3)	$20
Post-Intervention (V4)	$20
Total Participant Compensation	**$240**

If, for any reason, e.g. technical or CT Payer vendor issues prevent the site study personnel from issuing the reloadable debit card, adding funds to the reloadable debit card, or making any other changes to the debit card, participants may be compensated through a gift card (e.g. Amazon eGift Card, Visa Gift Card, or similar vendor). In such cases, participants are expected to read the associated terms and conditions for the respective gift card. For Amazon eGift Cards, the participant must accept the eGift Card through their email; participants will be

notified of this requirement prior to sending the payment, and will be asked to provide verbal consent to receiving payment in this method.

If the participant does not complete the study or withdraws early for any reason, the participant will only be compensated for the study visits and/or treatment sessions they have completed.

All participants will receive compensation for the *Screening* Visit (V0) after the end of the visit, regardless of eligibility. For participants who are loaned a digital device for the duration of the intervention periods, compensation for all study activities completed from V1 through V4, including the intervention periods, will occur after the participant returns the loaned device to the site study personnel. If participants are unable to meet with site study personnel in person to return the device, the participant will be sent a pre-paid label and box (if necessary) to return the digital device at no cost to them. Participants who withdraw from the study will be compensated for all study visits they have completed once the loaned device has been returned to the site study personnel. For participants who do not return the device, all forms of appropriate means and communication (e.g., phone contact, email, mailed letters) will be used in an effort to retrieve the study device. Study devices loaned to participants will have a mobile device management (MDM) platform installed that will enable the Posit Science Property Management team to remotely deactivate the device so that it is unusable, and/or erase the contents of the device. Only when a device has been reported lost or stolen, the Posit Science Property Management team may access the geolocation of said device through this MDM platform to lock, erase, or restart the device, ensuring participant data is protected and inaccessible. Participants who do not return the study device will receive their compensation after site study personnel have exhausted all means of contact in an attempt to return the device (a maximum of three months after the end of study participation). Participants will not face any legal or financial retribution for failure to return the study digital device.

During the consenting process, participants will also be requested to fill out an emergency contact form. This form will detail primary and secondary emergency contact information. If the participant agrees to fill this form out, the participant authorizes the site study personnel to contact the primary or secondary emergency contact in case of an in-office emergency. Participants will also be asked to sign a Release of Information authorizing site study personnel to communicate with the participant's clinical care provider to confirm and discuss their diagnosis, symptoms, treatment status, study participation, and to discuss any safety concerns that are discovered during the course of the study. Site study personnel may request relevant records from the participant's care team if there is a relevant health concern (e.g., hospitalization for psychiatric reasons). Participants will be notified before site study personnel contacts their care team for any reason.

A copy of the informed assent/consent will be provided directly to the participant and/or parent/legal guardian, a fully-executed copy will be retained in a secure manner at the recruitment site and be available for inspection at the site upon the request of representatives of the reviewing Institutional Review Board or other relevant regulatory agencies. No study activities will take place prior to completion of the assent/consent process. The copy of the consent form provided to the participant will include telephone and email contact information for the site study coordinator and the site PI. At any point during or after completion of the study, the participant may contact the site study coordinator, site PI or the reviewing Institutional Review Board to obtain additional information regarding his/her rights as a participant. No participant will be under legal commitment at the time of their consent or during their participation in the study.

Screening Procedures

Following informed consent, potential participants will go through a set of structured interviews and short neuropsychological assessments and provide basic demographic information to evaluate their suitability for the study given the inclusion/exclusion criteria. The screening procedures include:

- Demographics and Medical History: A structured clinical interview will be used to collect key demographic and medical history information, including medical diagnoses or conditions that may be grounds for exclusion (e.g., history of psychotic or seizure disorders, or ongoing or recent chemotherapy) and age.
- Confirmation of Autism Spectrum Disorder (ASD) diagnosis via medical/clinical records and/or standardized assessments (e.g., Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) or Autism Diagnostic Interview - Revised (ADI-R)).
- Cognitive Status: Participant's IQ must be greater than 70 on the Wechsler Abbreviated Scale of Intelligence (WASI-II) or on a comparable measure in their medical/clinical records, to be eligible for enrollment. For adult participants, the UBACC will serve as an additional measure to assess cognitive status. Participants scoring less than a 14 (75%), may be indicative of compromised cognitive status. Those that cannot pass the UBACC will not be eligible for enrollment.

Study Procedures/Research

Study Procedures: Participants will flow through the study in the following manner:

1. *Consent and Initial Screening Visit (V0)*: Site study personnel will discuss study goals, activities, and requirements with the parent/legal guardian and/or potential participant; complete the informed consent discussion, and if/when appropriate the potential participant will complete assent/consent to join study. Following assent/consent, site

study personnel will perform diagnostic assessments and interviews and assess inclusion/exclusion to determine if the participant is eligible for enrollment. Duration: ~2-3 hours remotely or in-person.

2. *Baseline Assessment (V1):* Following enrollment, the participant will perform all social/cognitive baseline characterization assessments and questionnaires prior to the intervention period. Duration: ~2 hours remotely or in-person.
3. *Randomization*: Participants will be randomized into one of three treatment arms.
4. *Digital device Set-Up and Proctored Application Use (V2)*: The participant will be oriented to the intervention activities and program application(s). Participants will also complete a series of digital assessments during this visit via BrainHQ. Participants with a compatible personal device that are willing to download the necessary application(s) for program use will have their device set-up at this visit and will be guided to schedule reminders for completing their study activities. Participants that do not have a compatible personal device, do not wish to use their personal device, or do not agree to configure their settings and download the necessary application(s) for program use will be loaned a digital device for the duration of the *Intervention and Program Use* period. Participants will be asked to sign a form acknowledging they have been loaned a study device. The study team will attempt to complete this visit on the same day as V1, but a separate visit may be scheduled, if necessary. Duration: ~30-60 minutes remotely or in-person.
5. *First Intervention Period and Program Use:* Participants who are assigned to receive CICADAS only will be engaged with the NB-SCT exercises for a total of 40 hours during the 16-week period. Participants who are assigned PEERS + CICADAS will be engaged with the NB-SCT exercises for a total of 40 hours and weekly 1-hour PEERS group sessions during the 16-week period. Participants who are assigned to PEERS + Active Control will be engaged with the Active Control app for a total of 40 hours and weekly 1-hour PEERS group sessions during the 16-week period. For PEERS group sessions, Site study personnel will review procedures and guidelines to group sessions and will ask the parent/legal guardian and/or participant to review and sign this form.
6. *Mid-Intervention Assessment (V3)*: Participants will be asked to complete the full battery of assessments performed at baseline.
7. *Second Intervention Period and Program Use:* Participants who are assigned to receive PEERS only will be engaged in weekly 1-hour PEERS group sessions during the 16-week period. The other arms will not receive any treatment during this period.
8. *Post-Intervention Assessment (End of Study Visit; V4):* After the *Second Intervention and Program Use* period is completed, the participant will be asked to complete the full battery of assessments performed at baseline to assess changes in performance. Duration: ~2 hours remotely or in-person.

Participants expressing interest in returning their device to its original settings will be instructed by site study personnel on how to delete study application(s) during this visit or at the time of study exit. Participants loaned a study device will be asked to return the loaned device at this visit. If participants were loaned a digital device to complete study activities at home and no longer wish to participate in study activities, including their post-intervention interview, site study personnel will attempt to coordinate with the participant to return the device at a time that is convenient for the participant. If the participant cannot be reached, site study personnel will send them a letter asking them to return the device along with a box with a return label. Participants will be invited to come back for a follow up visit in this letter, but also reminded that they are free to no longer participate in the study. Site study personnel may also send this letter to participants who completed all study activities but forgot to return the device and are unable to coordinate with site study personnel to return it.

9. *Exit Survey* (~10 minutes): Participants will be asked to fill out an online exit survey to rate enjoyment, usability, perceived benefits, and ease of fit into schedule.

Assessments.
The complete assessment battery will be performed at the pre-intervention assessment (*Baseline Assessment*, V1) visit, at *Mid-Intervention* assessment (V3) visit and at the post-intervention assessment (*End of Study*, V4) visit. For a full list of all assessments and administration times, please direct your attention to the *Description of Assessments* or *Appendix I*. We will use assessments of functional abilities to determine the degree of transfer of benefit to real-world experience (e.g., symptoms, social functioning, quality of life).

All assessments will be administered to all participants; alternate forms of the assessments will be used when available to mitigate test-retest effects. Performance on all measures will be scored, submitted into the study database, and monitored for accuracy and integrity. Any discrepancies in scoring will be resolved by referring to the raw data collected during the assessment visit(s).

Description of Assessments

Clinical and Neuropsychological assessments and characterization
The study will employ empirically validated assessment measures specific to ASD. Collectively, we have chosen a battery based on five key criteria (when possible), including 1) existing standardization, to ensure reliable data collection procedures, 2) sensitivity to the impairment typical of this study population, 3) normative data availability, 4) reasonable test-retest stability (i.e., to control for potential participant improvement through strategy learning over repeated measures) for use in a treatment trial with two repeated measures, and 5) good

sensitivity to change following remediation. Several measures will be used to provide gross clinical characterization.

Cognitive Function

At *Screening* Visit (V0): Cognitive status will be determined using the WASI-II or a comparable measure in their medical/clinical records. An IQ > 70 is required to enroll in the study. Adult participants will undergo an additional cognitive assessment, the UBACC. Participants must score within the normal range; participants who cannot pass the UBACC will not be eligible for enrollment.

For *Baseline* (V1), *Mid-Intervention* (V3) and *Post-Intervention* (V4) Visits: We will assess cognition directly by administering the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2), Mind Bender, and PsyToolkit's Eriksen Flanker and Wisconsin Card Sorting Tasks.

ASD-related Behaviors

We will assess ASD-related behaviors by administering the Repetitive Behavior Scale - Revised (RBS-R); Social Responsiveness Scale, Second Edition (SRS-2); Achenbach System of Empirically Based Assessment (ASEBA) - Age Dependent: Child Behavior Checklist (CBCL - parent report), Youth Self Report Form (YSR), Adult Self-Report (ASR), or Adult Behavior Checklist (ABC)

Social Cognition

We will assess social cognition and skills by administering the Dynamic Affect Recognition Evaluation (DARE), the Social Skills Improvement System - Rating Scales (SSIS-RS), and the Test of Adolescent Social Skills Knowledge (TASSK).

Sensory Processing

We will assess sensory processing by administering the SCAN-3:A Tests for Auditory Processing Disorders in Adolescents and Adults and the Brain-Body Center Sensory Scales (BBCSS).

Quality of Life

We will assess quality of life by administering the Pediatric Quality of Life Inventory (PedsQL).

Intervention Embedded Assessments

All participants, regardless of treatment group, will complete the ten sensory processing assessments before and after the first intervention period.

The primary outcome measures, including digital assessment completion rate, NB-SCT program adherence, usability ratings, reported adverse effects, and overall program completion rate will be used to assess feasibility, acceptability and usability of CICADAS app.

Secondary outcomes measures include baseline, mid-intervention, and post-intervention assessments as well as the weekly number of initiated or reciprocated social gatherings related to or in addition to PEERS assigned social activities.

Description of Protocol Devices (Software Program)

This study employs three digital-device delivered interventions: CICADAS app, Active Control app, and PEERS. Participants assigned to receive CICADAS only will be engaged in NB-SCT exercises for a total of 40 hours during the 16-week period. Participants who are assigned to receive PEERS only will be engaged in weekly 1-hour PEERS group sessions led by a PEERS clinician during the 16-week period. Participants who are assigned PEERS + CICADAS will be engaged with the exercises for a total of 40 hours and weekly 1-hour PEERS group sessions during the 16-week period. Participants who are assigned PEERS + Active Control will be engaged with the Active Control app for a total of 40 hours and weekly 1-hour PEERS group sessions during the 16-week period.
Several elements of flexibility are allowed in the schedule to accommodate the challenges that adolescents with ASD may face:

- *Location of Use:* Some participants may experience barriers to receiving treatment, including geographic location, long waiting lists, and the requirement to take time off from school for clinic visits. This intervention is available either remote and/or in-person. Every effort will be made to schedule the weekly group sessions at a time that is most convenient for the participants. The assessments and exercises are digitally-accessible, allowing participants to complete them at different locations, as convenient.
- *Variable Number of Total Sessions:* Given fatigue (common in this population), commitments to non-study activities, health issues and/or reintegration into school, work and home life, we expect that some participants will not be able to complete the weekly PEERS sessions for 16 weeks. To accommodate this, we will be understanding of their circumstances, recommend that participants complete as many sessions as their schedule permits, and explain that the results of the trial may benefit from frequent and consistent involvement in group sessions. The site study coordinator may offer their support to work with the participant on a training schedule that is feasible, given participant's current life circumstances, as appropriate. To ensure a time-bounded study commitment, after 16 weeks such participants will perform their mid-intervention assessment (*V3*) or post-intervention assessment (*End of Study*, V4) visits, given that they have met the minimum number of sessions required to complete this visit.

- *Extra Time:* Under special circumstances, PEERS session(s) may be paused for 1 or more weeks. This may occur if the PEERS Clinician is unable to conduct the session and no alternate PEERS Clinician is available to conduct the session. In such cases, the intervention will be extended by the number of weeks it has been placed on hold. Participants will resume the PEERS sessions such that all 16 sessions intended for the intervention are delivered to participants.
- *Cessation of Program Use While Continuing Participation in the Study:* In some cases, a participant may wish to stop or minimize use of the program, while remaining in the study. Potential reasons for this decision might include changes in school or work circumstances, changes in residence, health issues, family/personal issues, or a lack of interest in program activities. While the participant will be encouraged to meet their weekly goals, in such cases, after discussion with the site study coordinator, the participant will be permitted to cease using the program and undergo the mid-intervention assessment (*V3*) or post-intervention assessment (*End of Study*, V4) visit, given they have met the minimum number of sessions required to complete this assessment.
- *Emergency:* All participants will be told how to contact the appropriate site study personnel in the case of an emergency.

Several of these options in aggregate are likely to lead to variation within a group and between groups with regard to the total number of sessions completed, and may cause an imbalance between the number of sessions completed within and between groups. Although this is not ideal, we believe that this is the correct approach given that such flexibility will allow more participants to join the study (compared to no program use flexibility), and reduce attrition. In addition, this approach has the value of more closely mimicking real-world use of the program, increasing the prospective validity of the study. We will continuously monitor the distribution of completed sessions and will consider modifications to the protocol (see Modifications to the Protocol) if it appears that this flexibility may be associated with meaningful differences. The data analysis plan is generally robust to variations in the number of sessions completed (see Data Analysis).

Each study participant will be remotely supervised by a site study coordinator. Participants may be contacted once per week by a member of the study team to discuss participant engagement with the CICADAS or Active Control apps or intervention activities, and contact may adjusted depending on each participant's needs. Based on our previous experiences with in-residence trials, we have developed protocols and training that will allow the site study coordinator and PEERS clinicians to establish rapport with participants, identify and tend to any barriers to program use or compliance (such as establishing reminders to complete assessments or reducing distracters in the environment), and to provide feedback and support

around performance. The site study coordinator and PEERS clinician will also be specifically trained to deal with specific issues that might arise with individuals with ASD.

Treatment Arms

Arm A: Participants assigned to Arm A will engage in CICADAS only for the first 16 weeks of the intervention period. After the completion of the first intervention period and the mid-intervention assessment (V3) visit, these participants will then be assigned to the PEERS only group for the second 16 weeks of the intervention period.

Arm B: Participants assigned to Arm B will engage in PEERS + CICADAS for the first 16 weeks of the intervention period. After the completion of the first intervention period and the mid-intervention assessment (V3) visit, these participants will then be assigned to No-Contact (no active intervention) for the second 16 weeks of the intervention period.

Arm C: Participants assigned to Arm C will engage in PEERS + Active Control for the first 16 weeks of the intervention period. After the completion of the first intervention period and the mid-intervention assessment (V3) visit, these participants will then be assigned to No-Contact (no active intervention) for the second 16 weeks of the intervention period.

Treatment Interventions

CICADAS app: Participants will complete sensory processing assessments and neuroplasticity-based social cognitive training (NB-SCT) exercises on a digital device for a total of 40 hours through BrainHQ. The CICADAS app captures user-specific sensory processing abnormalities (SPA) through 10 brief computerized assessments. Participants will complete these sensory processing assessments before and after the first intervention period. The data from these assessments guide and personalize the delivery of 13 NB-SCT exercises. The NB-SCT exercises are adaptive with the task difficulty adjusting on a trial-to-trial and session-by-session basis to the abilities of each individual. Participants will need to log in to access these assessments and exercises using a study provided username that contains no personally identifiable information.

CICADAS Assessments and Training Exercises			
Sensory Processing Assessments		Neuroplasticity-based Social Cognitive Training Exercises	
Sound Sweeps	Auditory Perception/Processing Speed	That Emotion	Go/no-go task*
Beep Seeker	Auditory Distractor Suppression	Stop Signal	Stop-signal task*

Fine Tuning	Auditory Distractor Suppression	Rule Switch	Set switching task*
Visual Sweeps	Visual Perception/Processing Speed	Emotional Faces	Stroop-like task*
Bubble Pop	Visual Multiple Object Tracking	Emotion Tracker	N-back task*
Mind Bender	Visual Task Switching	Letter Identification	Dot probe task*
Tap The Emotion	Emotion Detection/Inhibitory Control	Say What?	Prosody theory of mind task
In the Know	Auditory Social Memory	Voice Choice	Prosody naming task
Face to Face	Emotion Match/Identification	Face Replay	Emotional memory task
Emotional Face	Emotional Conflict Resolution	Gaze Match	Gaze matching task
		To-do List Training	Verbal working memory task
		In the Know	Auditory social memory task
		Auditory Ace	Auditory working memory task
*using emotionally expressive faces and emotional valence words			

Active Control app: Participants will play previously-vetted and popular casual video games for an overall duration that is time-matched to the CICADAS program. These games are designed to *not* actively engage the neural systems that underlie ASD. With this kind of control, the current study will be able to assess convergent validity (i.e., that exercises that should improve cognitive function, in fact do) and discriminant validity (that exercises that should not improve cognitive function, in fact don't). We will use control games that are designed to be a face-valid approach to cognitive training, that can be described to participants as a valid approach for improving brain health, and that support a matching of the

expectation-based influence on performance in neuropsychological outcome measures. Participants will also complete the sensory processing assessments before and after the first intervention period.

We will carefully match the CICADAS program and the active control program in overall program use intensity, modality (visual), mode of delivery (supervisor portal), time-spent attending, delivery of rewards, and overall engagement; and provide a comparison group that matches the CICADAS group on the aforementioned attributes, but without the key elements specific to improving the neuro-modulatory control of the brain. Variety and novelty are critical to maintaining participant engagement in the active control group. Here are some examples of the games below:

- Lineup Four: Line up four chips in a row before your opponent.
- Bricks Squasher II: Move a paddle and bounce the ball to destroy the bricks.
- Gems Swap: Form a line of 3 or more identical gems by swapping their positions.

These computer games are fully developed, widely believed to be cognitively beneficial, are applied in graded levels in training, and are rated E (for everyone) by the Entertainment Software Rating Boar.

PEERS: Participants will be asked to attend weekly 1-hour group sessions led by a PEERS clinician. Each PEERS group session will consist of a minimum cohort of 3 participants and will meet as a group during the 16 week period either remote and/or in-person. The PEERS clinician will create a video-conferencing room open to cohort participants who meet remotely using Zoom application. The group sessions will be scheduled and monitored by the PEERS clinician. PEERS teaches how to solve real-life social dilemmas, appraise affect and social contexts, and initiate and maintain conversations while receiving feedback from peers and clinicians. Additionally, structured practice interactions during socialization activities (e.g., playing sports, games, etc.) are integrated into the curricula. Adjustments may be made during COVID-19 to allow for a more appropriate treatment given current shelter-in-place and distance-learning procedures that may not allow for replication of the traditional protocol.

Application Security

CICADAS and Active Control apps: All usage and progress data collected through the CICADAS and Active Control applications are encrypted then transmitted to a central server. Data is encrypted in transit and at rest, and access is limited and audited. Data collected through the platform will not include geographic information. IP address data is stored only in memory and in request logs, and is used for technical support and troubleshooting, but not persisted with the participant's data. However, data as it relates to dates that assessments are completed is collected and stored. On the server, the data are available for review by the un-blinded members including, site study coordinator, Posit Science study team, and/or other

study personnel, through a secure web portal. The study team in particular will use the secure web portal to regularly check on usage and progress of each active participant to customize their weekly phone/in-person to provide helpful guidance and coaching.

Zoom: This platform allows participants to communicate with others via the app without having to share their full name, mobile phone number or email to do so. Participants will choose whether to use their first name or an alias. In order to access the Zoom meeting, participants will be required to enter a passcode for their specific meeting. Once the participants enter the meeting, they will be operating within the Zoom HIPAA-compliant digital environment, and data that are produced, transmitted, and shared among users will be exclusively visible/readable to other participants and study staff. These data will include personally identifiable information–such as faces, first names or aliases, biographical and medical information–similar to what happens during all in-person group therapy sessions. Participants will be aware that the research team will have access to the group chat history and will be monitoring its contents throughout the intervention periods. As such, participants are informed that any personally identifying information voluntarily shared on this platform will be viewed by study staff. More information about how Zoom protects privacy can be found here:
https://zoom.us/en-us/trust/privacy.html

Laboratory Specimens

There are no laboratory specimens collected for this study.

Sample Size Justification

Attrition rates from the ASD pilot study conducted at University of Minnesota were > 30%. This high dropout rate can be ascribed to design issues, in that: (1) the sample recruited for the pilot consisted of adolescents who were not intrinsically interested in long-term treatment options for ASD, unlike the current target (adolescents already seeking PEERS); and (2) study coordinators had not been formally trained on how to keep participants engaged in a remote cognitive training intervention. By recruiting adolescents already seeking PEERS and by rigorously training our staff, we expect retention rate for this project to be in line with those of 1) cognitive interventions delivered to adolescents with ASD;4,5 2) PEERS groups.6 We project a 15% non-completion rate estimate for this study. We will recruit 56 participants to obtain 48 study completers. As the primary aim of this study is to gather information about the feasibility, acceptability and usability of this approach, the sample size of N=56 is set primarily for practical reasons and not driven by hypothesis testing. This size will, however, provide data to power a subsequent pivotal efficacy trial in Phase II, and will provide the field validation data required to submit CICADAS to the FDA as a medical device for such a trial

under the 510k de novo process. We are confident that we will meet our recruitment goals with these resources in place.
Of interest to the design of our proposed trial, despite randomization to the auditory or visual training conditions, 73.2% of participants who were assigned to the Visual condition at BL completed the training whereas only 38.5% of participants who were assigned the Auditory Condition completed the program. This highlights the importance of personalized intervention programs that take individual differences (e.g., auditory sensitivity) into consideration. In fact, several participants who chose to discontinue attributed their decision to an aversion to the auditory stimuli used in the computer programs. Baseline SCAN Competing Words Test scores were significantly related to whether individuals randomized to the Auditory or Visual NB-SCT Modules completed their training [$F(2,23) = 6.331$, $p = 006$]. In other words, participants randomized to the Auditory NB-SCT who did not complete their program had significantly more auditory processing difficulties than those who completed the program.

Data Management

Data collected in this study may include paper forms for consent/assent forms and some assessments from clinician- or psychometrician-administered structured interviews, neuropsychological or functional assessments. Other assessments will be administered remotely and collected electronically through REDCap servers or the program platform hosted on Posit Science servers. Fully executed consent/assent forms completed site study personnel and securely stored at the site. With the exception of dates that assessments are completed, personally identifying information collected will not be stored with study assessment or performance data on the CICADAS and Active Control apps on Posit Science servers. Personally identifying information voluntarily disclosed by participants on the Zoom platform during the intervention will be accessible to the research team. Participants are informed that the research team will be monitoring their chat history on the Zoom platform. Prior to entering the participant's study record, direct identifiers (names, email addresses) will be redacted. De-identified, study-related data collected on paper and will be recorded into a secure, web-based electronic case report form (eCRF). This system meets all relevant privacy and security standards for electronic clinical trial data entry and storage, as well as the Health Insurance Portability and Accountability Act (HIPAA) standards for confidentiality and privacy.

Following consent, each participant will be assigned a standardized Participant Identification Number (PIDN) composed of digits to identify the study and 3 digits to identify the participant. The digits will begin with "001" for the first consented participant and ascend thereafter. All eCRF data entry will be de-identified, using the PIDN only and not the participant name, but will include the date of the assessment administration.

Participants may email site study personnel with questions or concerns, or to make arrangements for study visits. If deemed significant and relevant to the participant's study record, de-identified emails may be saved to the participant's study file. To de-identify emails, all direct identifiers (name, email address, date of birth, etc.) will be redacted from the email in PDF format. Site study personnel will place black bars over any directly identifying information. The redaction will be verified by a secondary staff member for accuracy and completion to ensure patient privacy prior to being uploaded for permanent storage. The dates of communication will be maintained in the emails to provide context for the conversation.

Site study personnel will transcribe and upload de-identified data and de-identified source documentation into the study database for the purpose of data monitoring. Periodic analysis of the data will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. PSC data management personnel and site study personnel will interact frequently throughout the study to accomplish the quality goals of the data management process through the below process.

Periodic analysis of each data field (across all cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. Particular attention will be paid to the following:

- *Data Cleaning:* All eCRFs are automatically reviewed to check for omitted data and data inconsistencies. These deficiencies are required to be resolved at the point of data entry to prevent errors from entering the system.
- *Data Editing:* Each data record is evaluated on a regular interval. Any discovered error is then referred to the Investigator Designee within the Electronic Data Management (eCRF) System via the Data Monitor. The Investigator Designee will review the queries and make the corrections through the eCRF system. All such changes are automatically logged to allow a complete audit trail and recovery to any point in the change log if required.
- *Data Update:* The cycle of data editing will be ongoing until all the data are clean. If further data entry or source documentation errors are discovered during review, the corrections will be made at that time through the eCRF system.
- *Data Back-up:* The eCRF system employs an automatic continuous replication system to ensure that all data including change logs and access logs are replicated to two independent remote servers. At any point, the system is capable of emitting the entire store of eCRFs as paper CRFs for offsite storage or auditing if required.

We will take all standard and appropriate steps to protect the privacy and confidentiality of participants in this trial. At enrollment participants will be assigned a PIDN as described above, and all study data collection derived from that participant will be coded by PIDN. All

eCRF pages, including those with demographic as well as assessment data, will have the PIDN on them rather than the participants name. Dates that assessments are completed and date of birth will be collected. Personally identifying information voluntarily disclosed by participants on the Zoom platform during the intervention will be accessible to the research team. Prior to entering the participant's study record, direct identifiers (names, email addresses) will be redacted. Accurate and complete study records will be maintained and stored in a confidential manner so as to protect the confidentiality of participant information.

The eCRF system runs on remote servers not physically accessible to any study staff; all electronic access to the eCRF system is logged and regularly reviewed for any inappropriate access. All study related paper materials will be stored in locked file cabinets inside of locked rooms when not in use. During remote procedures, study personnel may shred the original paper documents after Posit Science has completed the data monitoring and reconciliation process and approved shredding of documents. Until documents are ready for shredding, they will be stored by the respective study personnel with limited access until the documents are shredded or transferred to the Study Site. All participant use of the CICADAS and Active Control programs will use a login based on the PIDN, and study programs will not collect or store any personally identifiable information on the laptop or on PSC servers, with the exception of dates that assessments are completed. Participants will choose whether to use their first name or an alias for the Zoom account.

We note this protocol does collect sensitive information, i.e. when assessing suicidal ideation, that may result in a reporting requirement to state or local authorities. The site is expected to follow standard institutional policies in such cases to ensure the protection of participants and proper reporting. If study personnel become aware of specific issues outside of the ordinary data collection procedures (e.g., child abuse) they will follow established institutional procedures already in place as appropriate for their local jurisdiction to report such knowledge.

Confidentiality

Participation in research may involve a potential loss of privacy. All records and documents pertaining to participation in this study will be handled as confidentially as possible. However, absolute confidentiality cannot be guaranteed.

All information, if collected on paper, will be kept in areas of limited access available to approved site study personnel only. Any physical records will be maintained in locked cabinets in locked offices, until the appropriate time at which documents may be shredded. Access to these cabinets will be limited to the study team.

Electronic data will be password protected and securely stored. The servers maintained by Posit Science are HIPAA compliant, secure servers that will require permissions from the study team to access.

Absolute confidentiality in group sessions is difficult to achieve irrespective of the delivery method (in-person, video-conference, etc.), as there is no guarantee that other group members will maintain confidentiality about sensitive information. However, in order to decrease the likelihood of breaches of confidentiality among group members, we will 1) provide informed consent about confidentiality; 2) educate group members about confidentiality; and 3) make the discussion of confidentiality an ongoing process.

- First, study participants will learn about confidentiality during the informed consent process. The consent form will clearly describe the roles and responsibilities of all parties and the limits of confidentiality.
- Second, individual sessions will be held between the site study coordinator and/or PEERS clinician and each participant to educate them regarding confidentiality prior to entering the intervention. Participants will be informed that 1) they have the right to choose an alias rather than their first name and decide at any point what information they choose to disclose; 2) the PEERS clinician will respect the patients' ability to choose what they disclose, and keep the promises of faithfulness and loyalty to all participants, including not revealing information participants disclose; 3) the PEERS clinician cannot promise that other group members will maintain confidentiality; 4) the PEERS clinician may have a legal obligation to break confidentiality in certain circumstances (e.g., child abuse), and those circumstances will be fully explained. The PEERS clinician will follow established procedures appropriate for their local jurisdiction to report such knowledge; 5) the research teams will be monitoring the Zoom contents, including chat history, throughout the intervention and as such any volunteered information that may be personally identifying will be available to research study monitors.
- Third, participants will be asked to read, sign and agree to be bound by a modified version of the American Psychological Association procedures and guidelines for group therapy (http://www.apadivisions.org/division-49/publications/newsletter/group-psychologist/2011/04/group-procedures.aspx), adapted for the target population, while in the intervention.
- Finally, during the first group session, the PEERS clinician will encourage group members to embrace the concept of confidentiality, making it their own rather than a mandatory rule.

Given that one of the goals of CICADAS is to enhance social functioning in individuals with ASD, we will not discourage group members from sharing contact information and befriending other study participants. Research shows that peer-to-peer interactions occur

naturally on social media platforms and serve many purposes, such as establishing new relationships, maintaining relationships, reconnecting with people, disclosing personal experiences of living with ASD, seeking and sharing information related to symptoms and medications.

Representatives of the Sponsor, the reviewing Institutional Review Board, and the National Institute of Health will be permitted to audit study-related data and related materials. Personally identifiable information will not be used in any study reports or publications; data contained in these will only be presented or published in aggregate form.

Disposition of Data

The following study records will be retained by the site for minimum of two years following the conclusion of the study:

1. signed participant informed consent forms,
2. patient medical records, including all significant diagnostic reports,
3. supporting documentation of all adverse events,
4. completed eCRFs, and;
5. study related correspondence and study reports.

Paper records from this study must be stored in locked areas of limited access. During remote procedures, documents will be stored by the respective study personnel in a safe location with limited access until the documents can be shred or transferred to the Study Site. Electronic data must be securely held with restricted access available to personnel on a need-to-know basis only. Google Team Drive access will be restricted to authorized study personnel by invitation only.

Sharing Research Results

Overall study results will be available to participants through ClinicalTrials.gov and when such results are completed and accepted for publication. At enrollment, information is collected that, if appropriate, we will share with the participant to ensure they are receiving appropriate health care (i.e. suicidality) as assessed by the C-SSRS. Any participant presenting a safety concern for any of these medical issues will be referred to ensure they are receiving appropriate treatment. We do not intend to share individual assessment data with participants, as the assessment battery is not intended to be the type of comprehensive battery a rehabilitation psychologist would use to guide treatment. Any participant interested in such comprehensive assessment will be referred to an appropriate clinician.

Foreseeable Risks, Risk Management & Emergency Response

Participation in the study presents minimal risk. The probability and magnitude of harm or discomfort anticipated in this research study are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Serious adverse effects from prior studies of the treatments under study have not been reported. The protocol details potential risks related to study participation and includes assessments of increased risk of suicidality.

The following foreseeable risks will be discussed with potential participants during the enrollment visit, as will the following measures taken to minimize such risks:

- *Diagnostic interview and self-report measures*. Participants may feel uncomfortable or embarrassed due to sensitive questioning about their psychiatric condition and medical history during the diagnostic interview or on self-report measures. Participants will be reminded during each appointment that their participation in the study is voluntary and that as such, they are not required to complete any assessments and may skip individual questions or assessments entirely.
- *Discomfort During Assessments:* Assessments may be fatiguing for some individuals, particularly for those with persistent cognitive symptoms. To minimize this potential discomfort, breaks are encouraged and scheduled within the session. In the event that a participant appears to be under undue strain, test sessions are discontinued.
- *Lack of Assessment Feedback:* Participation in this study does not include feedback to participants on their individual assessment results. Though participants are informed of this policy during consent, some participants may find the lack of feedback to be frustrating.
- *Discomfort During Intervention/Program Use:* The following risks may be reasonably anticipated as the result of intervention and/or program use: fatigue, mood complaint, headache, tremor, eye strain, neck/shoulder discomfort, leg/hip discomfort, arm/wrist discomfort, back discomfort, headache and sleep difficulty. To minimize the fatigue participants are encouraged to sit ergonomically correctly while completing study activities on their device. The program is also designed to be entertaining and enjoyable. In addition, assessment and self-report sessions may be paused at any time and participants are encouraged to take breaks.
- *Other Risks:* Although it has not been previously documented, it is possible that the use of the investigational program or participation in the study activities may cause symptoms to worsen. There may also be risks related to the use of the program that are unknown at this time.

- *Loss of Privacy*: The most significant risk to the participants are those that would follow a breach of confidentiality and the disclosure of clinical information. Participation in any research study, including this one, may involve a loss of privacy, and absolute confidentiality cannot be guaranteed. Procedures designed to maintain data confidentiality include (1) formal protocol training sessions for all study team members emphasizing the importance of confidentiality, (2) adherence to specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants. One reason for breaking confidentiality is that the study personnel are required by law to report cases of physical or sexual abuse to local law authorities; and another is that despite all procedures, an error may occur. To mitigate this risk, data forms that include identifying information, with the exception of dates assessments are completed, date of birth, and dates associated with other data collected, and personally identifying information volunteered by participants in the Zoom chat forum, will be kept in locked cabinets or secure servers at the site, and accessible only to authorized study personnel. Only the unique ID number, assigned by the study coordinator, will represent participants during participation in the study. In the Zoom platform, participants will have the choice to self-identify with their first name or an alias. To facilitate tracking, a password-protected computer file will be maintained containing the identity of participants, their ID numbers, and contact information. This file, however, will contain no clinical data. Electronic data will be password protected and stored on a secure network. All data keys will be stored separately and securely. Only study personnel will have access to the study data. No participant names will be used in study reports or publications.
- *Risks of Email Communication*: This study will rely on the use of email communication between study personnel and research participants as part of their participation in the intervention. Site study personnel may be expected to email participants about their upcoming appointments, provide weekly updates on program usage, or communicate other important study information. Participants may also ask questions of site study personnel using email. There are risks associated with email communication, and these risks increase when emails are sent without an encryption service. Risks of sending or receiving unencrypted emails include, but are not limited to:
    - Others can intercept messages
    - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages

- A copy of the message may be saved on a device or computer system, even if it is deleted
- If an email address is not typed correctly, it can be sent to the wrong person
- Emails can spread computer viruses
- Others may be able to access messages on devices that were lost, stolen, or thrown away
- If a participant changes emails without notifying site study personnel, they may miss communications.

Participants will be encouraged to report any adverse effects occurring during the duration of the study to the study point of contact.

PSC does not provide compensation for research-related injuries and will not reimburse or pay medical expenses for the treatment of research-related injuries.

Although there is little chance for a study-related emergency, the site PI and site study personnel are required to follow institutional standard operating procedures for obtaining emergency care or treatment for adverse effects requiring such. This study has adequate personnel and equipment to respond to expected adverse effects, and maintains working knowledge of the nearest treatment facilities available to patients enrolled into this study.

Potential Benefits

Two levels of benefit will be described to participants:

1. Benefit to Science: Results from this study will directly benefit the applied science in ASD. Understanding if the scientific design principles of CICADAS drive superior outcomes to current evidence based treatments will provide considerable insight to scientists and clinicians working in ASD.

2. Benefit to Participants: This study has the potential to directly benefit the participant, in terms of improved social functioning. We will emphasize that this is the level of benefit that is most speculative in this study, and that potential participants in any randomized controlled trial should join if the benefits to participants like them and to science from the overall trial results are compelling to them, and should not expect that the trial provides treatment benefits as such.

Study Personnel

Key study personnel at PSC include:

- Principal Investigator (Dr. Lee): responsible for the overall design of the study protocol and data analysis plan as well as the eventual publication of the result (with input and authorship from all investigators. She is also responsible for the execution of the study protocol, and coordinating activities with all PSC and UMN staff participating in the trial. Additionally, Dr. Lee will monitor, flag and/or remove inappropriate content on the Zoom chat and report and discuss the content with the appropriate team members, including the PEERS clinician(s).
- Sponsor Study Coordinator is responsible for assisting the PI with the execution of the study protocol and for data management. The sponsor study coordinator will also be responsible for monitoring all submitted data for consistency and integrity, monitoring, flagging, removing and/or discussing the Zoom chat content with the appropriate team members, including other PEERS clinician(s). Additionally, they will responsible for discussing all qualifying criteria with site study personnel, leading virtual training sessions, and holding meetings with the site study personnel. The sponsor study coordinator will be responsible for ensuring that the site meets regulatory compliance requirements and executes the protocol, as IRB approved.

Dr. Lee and research staff at PSC disclose a conflict of interest: all are paid employees of PSC and shareholders, and could benefit if this intervention for ASD is shown to be an effective treatment in this trial.

This conflict will be mitigated by ensuring that the complete investigator team, including Dr. Lee, and other PSC study personnel have joint and overlapping responsibility for the design of the protocol, the execution of the protocol, the *a priori* design of the data analysis plan, the execution of the data analysis plan, the interpretation of the study results, and the authorship of publications emerging from the study. In addition, this conflict of interest will be disclosed to all study participants, and through standard mechanisms for all publications.

Key study personnel at UMN include:

- Principal Investigator (Suma Jacob): responsible for the overall execution of the study protocol at the Study Site, including overseeing participant recruitment, enrollment and intervention delivery in conjunction with the site study team for this clinical trial. She will provide support and coordinate activities between PSC and UMN staff participating in the trial. She will be involved in the data analysis as well as the eventual publication of the result (with input and authorship from all investigators). Additionally, she will ensure that the site meets regulatory compliance requirements and executes the protocol, as IRB approved. Dr. Jacob will be blinded to participant randomization assignments.

- Site Study Coordinator is responsible for assisting the Site PI with the execution of the study protocol, recruiting, screening, enrolling and monitoring participant progress when active in the study. They will also be responsible for entering data into REDCap, reviewing data for consistency and integrity, reconciling data queries, and may randomize participants. Site study coordinator may serve as a back-up PEERS clinician and may be responsible for removing and/or discussing the Zoom chat content with the appropriate team members, including other PEERS Clinician(s) and the Posit Science research team. Additionally, they will assist in ensuring that the Site meets regulatory compliance requirements and executes the protocol, as IRB approved.
- Site Clinical Assessor will serve as the blinded psychometrician and clinical rater. They will conduct eligibility and clinical assessments with participants and will be blinded to their randomization assignment.
- PEERS clinician will lead the PEERS group sessions. For remote group sessions, they will monitor the Zoom forum and may be responsible for removing and/or discussing the Zoom chat content with the appropriate team.

Blinding

Un-blinded Roles: PEERS clinicians and the site study coordinator are un-blinded in order to lead group sessions and support for participants using their assigned programs. They will be distinct from staff administering and scoring assessments. Additionally, designated personnel that are un-blinded may not participate in the assessment and evaluation at Mid-Intervention (V3) or Post-Intervention (V4) assessment visits of study participants.

Blinded Roles: All site staff responsible for the administration and scoring of participant assessments visits conducted after randomization will remain blinded to participant treatment. The Site Principal Investigator will be required to complete a Delegation of Authority Form, indicating which activities individual research team members will be authorized to complete. Principal Investigators will also remain blinded.

Depending upon the extent to which they are responsible for data collection and/or entry, *site study coordinators* may or may not remain un-blinded to participant treatment. This will be clarified on a site-by-site basis and will be noted on the Site Principal Investigator Delegation of Authority Form.

To prevent un-blinding, the following will occur:

1. The treatment arms will be identified as "Arm A, Arm B, and Arm C."

2. Participants will be reminded not to discuss details related to treatment with blinded psychometricians and/or clinical evaluators during the informed consent process as well as prior to initiation, and at the conclusion of, each assessment visit;
3. Site study personnel will be instructed to not discuss details of either treatment arm during open participant groups or forums outside of the assigned group sessions or cohort discussions;
4. Site study personnel will be required execute the protocol in a manner that minimizes the possibility of accidental un-blinding of psychometricians or clinical evaluators (e.g. unintended viewing of treatment sessions);

Research Monitor

This is a minimal risk protocol. There is no significant risk to using either of the web-based programs in this study, beyond the minor discomfort and tedium risks noted above. Previous studies in healthy aging, schizophrenia, and spatial neglect have not noted any significant adverse events arising from program use. Nonetheless, to follow best practices for treatment trials in medical indications, we will employ a central Research Monitor to review all unanticipated problems involving risk to participants, serious adverse effects, and any participant deaths associated with the protocol, and provide an unbiased written report of the event within ten calendar days. The research monitor will comment on the outcomes of the adverse event and relationship of the event to the protocol or test article. The research monitor will also indicate whether they concur with the details of the report provided by the PI. Reports for events determined by either the PI or Research Monitor to be possibly or definitely related to participation, and reports of events resulting in death will be promptly forwarded to the IRB.

Withdrawal from the Protocol

Study participants may withdraw from the study at any time, for any reason, or for no stated reason. We anticipate that a common reason for study withdrawal will be the time required to complete the intervention. For participants seeking to withdraw for that reason, we will offer the alternative of discontinuing the intervention and scheduling and completing the post-intervention assessment (*End of Study, V4)* visit, given they have met the minimum sessions required to complete the assessment visits. The data analysis plan is structured so that their data will be valuable even if they do not complete the intended number of sessions. Participants who still wish to withdraw following that option will withdraw. Other than time required to use the program, we do not anticipate any common reasons for withdrawal that we will plan for in advance.

In rare cases, a Principle Investigator may decide to prematurely discontinue a participant's involvement in the study for any of the following reasons:

a) Safety,
b) Participant non-compliance,
c) A change in circumstance that would prevent completion of protocol-required assessments,
d) Participant relocation to an area that, due to great distance, would prohibit a participant from receiving follow-up at the study site,
e) Participant displays inappropriate behavior toward study staff members or other participants,
f) Participant is hospitalized for psychiatric reasons;
g) Loss of funding, or;
h) A clinical determination, by the Principal Investigator, that continuation in the study is not in the participant's best interests.

Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by arranging for the site study coordinator or PEERS clinician to recover the digital device (if it has been issued to the participant), conducting an informational interview with the participant to understand the reasons for study withdrawal and identify any issues with study conduct or adverse events that are relevant, and arrange study compensation for sessions that the participant completed.

Modifications to the Protocol

Any significant changes to the protocol, including changes to inclusion/exclusion criteria, changes to assessments, changes to recommended intervention and/or program use, changes that could potentially increase risk to study participants, and additions or removals of key personnel and/or recruitment sites will have to be approved by the PIs. Changes requiring approval by the Institutional Review Board will be submitted for review in the form of a protocol amendment or revision prior to implementation.

Protocol Deviations

Protocol deviations will be noted and recorded by study staff (PI, Study Coordinator, Psychometrician, or PEERS Clinician) if they detect the deviation. All protocol deviations will be reviewed by the Sponsor PI (Hyun Kyu Lee) on a monthly basis and must be signed off by the Site PI; any such deviations suggesting systematic problems with the protocol procedures as implemented by the site will be reviewed and corrective action determined and implemented by the site.

Reporting of Serious Adverse Effects & Unanticipated Device Effects

The CICADAS protocol has minimal risk, and previous studies of similar approaches in psychiatric populations have not reported significant adverse events arising from intervention

and program use. Additionally, computerized treatment studies using Posit Science software in healthy aging, schizophrenia, and TBI have never reported adverse events attributable to study activities. Nonetheless, to follow best practices for treatment trials in medical indications, we will employ a central Medical Research Monitor to review all unanticipated problems involving risk to participants, serious adverse events, and any participant deaths associated with the protocol, and provide an unbiased written report of the event within ten calendar days. The Medical Research Monitor will comment on the outcomes of the adverse event and relationship of the event to the protocol or test article. The Medical Research Monitor will also indicate whether they concur with the details of the report provided by the study staff member. Reports for events determined by designated study personnel, i.e. Medical Research Monitor, to be possibly or definitely related to participation, and reports of events resulting in death will be promptly forwarded to Western IRB. Further, serious adverse events attributable to study activities and/or the intervention and/or program use, will be documented and reported immediately to the Western IRB. An event that is serious must be recorded on the case record and requires expeditious handling to comply with regulatory requirements. In the event that a patient becomes ill or injured as a direct result of participation in the project, necessary medical care will be made available.

The site study coordinator and PEERS clinician will ask about any deterioration in symptoms during each contact with participants, and will be alert to any volunteered episodes of suicidality. All events of this nature will be documented on a standardized form and will be classified by the PI to their degree of seriousness and their relationship to the study protocol. Participants will be referred to appropriate clinical care should there be any concerns for safety or increasing symptoms. If deemed clinically necessary, the PI may elect to remove participants from the study if they find that it is no longer in the participant's best interests to continue participation in the study.

Finally, we will also conservatively follow guidelines for medical devices (i.e., computerized assessments) in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in The Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with, a device.

Continuing Review and Final Report

In accordance with NIH SBIR guidelines, a continuing review report(s) as well as a Final report will be submitted via eRA Commons.

The knowledge of any pending compliance inspection/visit by the FDA, Department of Health and Human Services Office for Human Research Protection, or other Government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any Regulatory Agencies, including legal or medical

actions, and any instances of serious or continuing noncompliance with the regulations or requirements will also be reported.

Surveys, Questionnaires and Other Data Collection Instruments

*Complete paper versions are available upon request.

Confirmation of ASD

The Autism Diagnostic Interview-Revised (ADI-R)
https://www.wpspublish.com/adi-r-autism-d-revised

Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2)
https://www.wpspublish.com/ados-2-autism-diagnostic-observation-schedule-second-edition

Cognitive Function

Wechsler Abbreviated Scale of Intelligence (WASI-II)
https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Cognition-%26-Neuro/Wechsler-Abbreviated-Scale-of-Intelligence-%7C-Second-Edition/p/100000593.html

Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2)
https://www.parinc.com/Products/Pkey/24

Mind Bender
https://www.brainhq.com/why-brainhq/about-the-brainhq-exercises/intelligence/mind-bender/

PsyToolkit's Eriksen Flanker and Wisconsin Card Sorting Tasks
https://us.psytoolkit.org/experiment-library/flanker.html
https://us.psytoolkit.org/experiment-library/wcst.html

ASD-related Behaviors

Repetitive Behavior Scale - Revised (RBS-R)
Lam KS, Aman MG. The Repetitive Behavior Scale-Revised: independent validation in individuals with autism spectrum disorders. *J Autism Dev Disord*. 2007;37(5):855-866. doi:10.1007/s10803-006-0213-z

Social Responsiveness Scale, Second Edition (SRS-2)
https://www.wpspublish.com/srs-2-social-responsiveness-scale-second-edition

Achenbach System of Empirically Based Assessment (ASEBA) - Age Dependent: Child Behavior Checklist (CBCL - parent report), Youth Self Report Form (YSR), Adult Self-Report (ASR), or Adult Behavior Checklist (ABC)
https://aseba.org/school-age/
https://aseba.org/adults/

Social Cognition

Dynamic Affect Recognition Evaluation (DARE)
Porges, S.W., Cohn, J.F., Bal, E., Lamb, D., & Lewis, G.F. 2016. The Dynamic Affect Recognition Evaluation software v2. Brain-Body Center for Psychophysiology and Bioengineering, University of North Carolina, Chapel Hill, NC.

Social Skills Improvement System - Rating Scales (SSIS-RS)
https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Behavior/Social-Skills-Improvement-System-SSIS-Rating-Scales/p/100000322.html#:~:text=The%20Social%20Skills%20Improvement%20System,problem%20behaviors%2C%20and%20academic%20competence.

Test of Adolescent Social Skills Knowledge (TASSK)
Laugeson, E. A., Frankel, F., Mogil, C. & Dillon, A. R. Parent-Assisted Social Skills Training to Improve Friendships in Teens with Autism Spectrum Disorders. *J. Autism Dev. Disord.* **39**, 596–606 (2009).

Gantman, A., Kapp, S. K., Orenski, K. & Laugeson, E. A. Social Skills Training for Young Adults with High-Functioning Autism Spectrum Disorders: A Randomized Controlled Pilot Study. *J. Autism Dev. Disord.* **42**, 1094–1103 (2012).

Sensory Processing

SCAN-3:A Test for Auditory Processing Disorders in Adolescents and Adults
https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Speech-%26-Language/SCAN-3%3AA-Tests-for-Auditory-Processing-Disorders-in-Adolescents-and-Adults/p/100000237.html

Brain-Body Center Sensory Scales (BBCSS)
https://www.phenxtoolkit.org/protocols/view/650401

Quality of Life

Pediatric Quality of Life Inventory (PedsQL)
https://www.pedsql.org/

Case Report Forms: this study employs both an electronic case report form system and a paper-based case report form system (i.e., source documentation records to support the EDC System).

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Appendix I. Table of Assessments

Assessment	Screening	V1	V3	V4
Informed Assent/Consent	X			
Demographics	X			
Medical History Questionnaire and Screening	X			
Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) or Autism Diagnostic Interview – Revised (ADI-R) – if needed	X			
Wechsler Abbreviated Scale of Intelligence (WASI-II) – if needed	X			
Medications, Screening	X			
PsyToolkit's Eriksen Flanker and Wisconsin Card Sorting Tasks		X	X	X
SCAN-3:A Test for Auditory Processing Disorders in Adolescents and Adults		X	X	X
Dynamic Affect Recognition Evaluation (DARE)		X	X	X
Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2)		X	X	X
Mind Bender		X	X	X
Pediatric Quality of Life Inventory (PedsQL)		X	X	X
Brain-Body Center Sensory Scales (BBCSS)		X	X	X
Repetitive Behavior Scale - Revised (RBS-R)		X	X	X
Social Responsiveness Scale, Second Edition (SRS-2)		X	X	X
Social Skills Improvement System - Rating Scales (SSIS-RS)		X	X	X
Achenbach System of Empirically Based Assessment (ASEBA) - Age Dependent: Child Behavior Checklist (CBCL - parent report), Youth Self Report Form (YSR), Adult Self-Report (ASR), or Adult Behavior Checklist (ABC)		X	X	X
Test of Adolescent Social Skills Knowledge (TASSK)		X	X	X
Medications, Since Last Visit		X	X	X
Adverse Effects		X	X	X
Unanticipated Adverse Effects	As needed			
Study Exit	As needed			

Appendix II. Sample Debit Card Information

Attached separately.