Statistical Analysis Plan

CICADAS: Care Improving Cognition for ADolescents on the Autism Spectrum

Protocol Number: PSC-0909-20

NCT04562688

Document Date: November 9, 2021

To achieve robust and unbiased results, data will undergo a rigorous quality control process to ensure consistency in scoring, coding and accuracy of data entry. Standard data quality procedures will be used, including double scoring and random spot checking of assessments and electronic data capture. Additionally, 20% of all data folders will undergo a random audit every 3 months in Phase I. The database will be designed to not allow illegal values in entry. Any outliers will be double-checked with the raw data for accuracy.

Design and Analysis Populations

The Phase I data analysis plan *a priori* defines a primary intent-to-treat (ITT) population, a set of secondary evaluation populations, a set of primary outcome measures, a set of secondary outcome measures, five evaluation time points, a criterion for statistical significance, and a statistical analysis methodology for secondary outcomes.

There are four *a priori* defined analysis populations, including a primary analysis population (i), a secondary analysis population designed to compare effect sizes in populations with no missing data (ii), a population who completed all study visits (iii), and a population that was randomized to access CICADAS.

i.*Intent to Treat (ITT) population:* This is the *a priori* primary analysis population, defined as including all randomized participants who attended at least one PEERS session.

ii.*Intent to Treat (ITT) Fully-Evaluable (FE) population:* This is a secondary analysis population, defined as including all members of the ITT population that complete a post-intervention visit. Note that a participant may complete a specific visit but have missing data for a test in which case the participant is in the overall FE population but does not contribute data to the FE population for that visit, e.g., the number of evaluable cases for a specific test on a specific visit may be smaller than the FE population for that visit because of missing data.

iii.*Intent to Treat (ITT) Completers (C) population:* This is a secondary analysis population, defined as including all members of the ITT-FE population who complete all intervention sessions. Note that the C population is a strict subset of the FE population; a person who completes the treatment but does not complete the post-intervention evaluation visit is not a member of the C population.

iv.Intent to Treat (ITT) CICADAS-Users (CU) population. This is a secondary analysis population, defined as all members of the ITT population who have received CICADAS+PEERS, except those who drop/withdraw post-randomization and pre-treatment.

Statistical Plan
Traditional Randomized Control Trials may not be the most effective way to test the efficacy of deeply-tailored, adaptive interventions. Instead, well-conducted, properly powered clinical trials that incorporate crossover design may be more useful in investigating how to optimize/enhance an evidence-based treatment (PEERS) with the experimental adjunct/primer (CICADAS). **Our trial defines: (1) three first stage treatment options; (2) a mid-study assessment point, (3) three second stage treatment options**.

After screening and enrollment, participants complete the full battery of assessments at baseline (Week 0). At Stage 1, **48** adolescents will be randomized to a 16 weeks of CICADAS only (Arm A) vs 16 weeks of PEERS + CICADAS (Arm B) vs 16 weeks of PEERS + Active Control. In order to reduce variance, we will employ a Stratified Permuted Block Randomization Design with strata defined by sensory processing symptoms to balance the number of individuals with SPA across each trial arm. After 16 weeks, the full battery of assessments will be administered again. Arms A, B and C will receive no contact for 16 weeks. At the end of the intervention, the full battery of assessments will be administered for a third time.

Evaluation Time Points
Week 0 –primary and secondary outcome measures are collected on all participants at baseline
Week 16 – primary and secondary outcome measures are collected on all participants
Week 32 – primary and secondary outcome measures are collected on all participants

Primary Outcome - Feasibility
Efforts will be made to assess all participants who have completed the minimum required intervention activities: For Arm A (CICADAS only), completing at least 1 hour of NB-SCT; for Arm B (PEERS + CICADAS), completing at least one PEERS group session and 1 hour of NB-SCT; and for Arm C (PEERS + Active Control), completing at least one PEERS group session and 1 hour of games.

As the main goal of this Phase I trial is to evaluate the feasibility, acceptability and usability of the CICADAS app, we will conduct an analysis of the following primary outcome measures in all ITT-CU participants:
1. Digital assessments completion rate. We expect that ≥80% of participants will complete the digital assessment battery at least twice during the CICADAS intervention:
2. NB-SCT program adherence, that is automatically tracked on the back-end data portal (percentage of training sessions completed). Based on our previous studies (CLIMB, MOODIFY, WASABI) and pilot, we expect that ≥70% of participants will complete 20 hours of NB-SCT;
4. Reported side effects (raw score). Based on our previous findings, we expect 0 adverse events due to program use;

5. Overall program completion rate. Based on previous findings from CLIMB and from the pilot in ASD, we hypothesize full program completion in ≥70% study participants.

Secondary Outcome - Preliminary Efficacy

The secondary outcome measures will be collected by trained personnel blind to treatment assignment at baseline, half-way through the intervention, and immediately after the treatment for all randomized participants. Weekly measures will capture the number of initiated or reciprocated social gatherings related to or in addition to PEERS assigned social activities.

Measures of Social Cognitive Functioning: We designed CICADAS to improve sensory processing abnormalities and social cognition in adolescents with ASD independently and to work in conjunction with PEERS to further enhance response to treatment. Our rationale is that many individuals are unable to process accurately information that underlies social and interpersonal cues. Thus, improving social cognition via targeted training of sensory processing abnormalities should confer an advantage to participants using CICADAS in conjunction with PEERS. The ability of CICADAS to prime the brain for PEERS will be measured through a subject-specific improvement in social cognition. Social cognitive functioning will be assessed a number of ways in order to gauge gains in social skills as well as ecological validity of the intervention. One of these measures will the PEERS-based Test of Adolescent Social Skills Knowledge (TASSK; Laugeson & Frankel, 2006), a 22-item survey that assesses the teen's knowledge about the specific social skills taught during the intervention. The TASSK is comprised of sentence stems and two possible answers. Total scores range from 0 to 22, with higher scores reflecting greater knowledge of the taught social skills. Additionally, we will include the performance-based Dynamic Affective Recognition Evaluation (DARE) test for socioemotional abilities in the participant as well as parent-report measures (SRS-2, SSIS-RS) in our outcome a battery.

The secondary statistical analysis methodology is a linear mixed model approach. First, we will investigate in the ITT population any differences in baseline demographic, characterization, outcomes variables. Any such factors that show trend level significant differences ($p < 0.1$) will be noted and used as covariates in the linear mixed model analysis. We will examine the data from each outcome measure using a linear mixed model with group and time as fixed factors, and covariates as necessary from the baseline analysis. Missing data will be handled with an iterative maximum likelihood procedure to optimally estimate model parameters. The key value for significance will be the group by time interaction factor for the model. Within-group effect sizes (Cohen's *d*) will be computed using the mean change scores for quantitative outcomes (end-of-treatment minus baseline) and the change score SDs.
With 48 participants fully evaluated, we will not have enough power to detect a treatment augmentation effect ascribable to CICADAS. However, data from this pilot trial will be used to power a pivotal RCT in Phase II, as they will allow to explore whether:

a) the concurrent delivery of CICADAS and PEERS for 16 weeks (B1-B2) induces greater improvements sensory processing, cognition, symptom reduction, social skills and behaviors, as well as quality of life, compared to CICADAS only (A1-A2) or PEERS + Active Control (C1-C2) – *preliminary efficacy of CICADAS as a treatment enhancer for PEERS;*

b) The concurrent delivery of CICADAS and PEERS for 16 weeks (B1-B2) induces greater improvements sensory processing, cognition, symptom reduction, social skills and behaviors, as well as quality of life, compared to the sequential delivery of CICADAS and PEERS (A1-A3) – *preliminary testing of CICADAS as enhancer vs primer;*

c) improvements sensory processing, cognition, symptom reduction, social skills and behaviors, and quality of life induced by the concurrent delivery of CICADAS and PEERS (B1-B2) are sustained after 16 weeks of no contact (B2-B3) – *durability of augmentation effects*.

To verify these experimental hypotheses, we will conduct the analysis based on the pre-intervention (baseline) and post-intervention data. The criterion for statistical significance is $p < 0.05$. Results with $p < 0.1$ will be described as trends.

Calculations from CRFs

The following calculations must be made from CRF data to create the required data tables. These calculations are performed automatically by scripts that operate on the tables from the EDC and produce processed data in new tables.

- **Cognition** *a priori* composite: PsyToolkit's Eriksen Flanker and Wisconsin Card Sorting Tasks, SCAN-3:A Test for Auditory Processing Disorders in Adolescents and Adults, Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2)
- **Symptoms** *a priori* composite: Child Behavior Checklist (CBCL), Repetitive Behavior Scale - Revised (RBS-R), The Social Responsiveness Scale, Second Edition (SRS-2)
- **Functioning** *a priori* composite: Social Skills Improvement System-Rating Scales (SSIS-RS), Pediatric Quality of Life Inventory (PedsQL)