Statistical Analysis Plan

Parent-Mediated Telehealth Intervention for Insomnia in Young Autistic Children

Version 2.0
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NCT07435740

Statistical Plan

Initial analyses will inspect data for errors, frequency, patterns of attrition, and missing data. Analyses will use SAS v.9.4 (Cary, NC) and CRAN R v.4.3 (Vienna, Austria) or higher. Statistical significance will be set two-sided at 0.05. The primary exposure is the randomized intervention, SPT versus SPE. We will follow ITT principles throughout, analyzing participants according to originally assigned groups, regardless of what treatment they received (if any) or attrition. Baseline child characteristics will be summarized overall and by the randomized treatment groups using means and standard deviations, medians and interquartile ranges, or frequencies and percentages, as appropriate. Given random assignment in the sample of up to 180, we do not anticipate group differences at baseline. We will confirm this assumption through two-sample statistical testing (e.g., t-tests and chi-square tests). If any baseline differences are noted between randomized groups, reported results will be adjusted for potential confounders through multivariable regression procedures and/or sample stratification. For all analyses, statistical assumptions regarding multivariate normality, heteroscedasticity, linearity, and disproportionate influence will be evaluated visually and confirmed statistically. If any of these assumptions are not met, we may perform some combination of data transformations, non-parametric piecewise or generalized additive models (GAMs), until the assumptions are met. All primary models will be presented unadjusted and adjusted for Vineland Adaptive Behavior Composite scores as a marker of cognitive ability.

Statistical Power for Aims 1a and 1b**:** Statistical power was calculated in PASS 2021 (Kaysville, UT) using two-sided tests and alpha=0.05. The primary study outcome (PAIRS) will be analyzed as a continuous measure to evaluate for a significant mean difference between randomized groups (SPT versus SPE) at study endpoint (Week 10). As noted, PAIRS scores range from 0 to 63, with higher scores indicating greater insomnia symptom severity. In a sample of 1,185 caregivers ascertained through the Simons Foundation database, the mean score for children with ASD (age 3 to 12 years) was 21.8±14.9. To recruit a sample of children with moderate or greater insomnia severity for the current study, we set a PAIRS threshold of $\geq$ 30 for inclusion (i.e., 70th percentile in the Simons Foundation sample). Given this threshold, the mean baseline PAIRS will be >30, and we estimate a standard deviation (SD) of 10 – i.e., lower than the SD observed in the large sample that included children across a full range of the scale. Our power analysis is based on a detectable minimum clinically important difference MCID of 5 points (one-half predicted SD), on the PAIRS between SPT and SPE cohorts. Using a two-level hierarchical general linear mixed model (GLMM) test for two means at study endpoint and assuming a within-participant PAIRS correlation of 0.5 across three study visits, a total sample of 130 participants (65 per group) provides 80% power to detect a 5-point difference at the 10-week study endpoint. This corresponds to a moderate effect size (Cohen's d = 5/10 = 0.5).
The proposed sample (up to 180) participants (90 per cohort) will increase our ability to examine moderators (see Aim 3) and account for attrition, which has been approximately 10% in a previous multi-site parent training trial for disruptive behavior in children with ASD delivered in-clinic (Bearss et al., 2015).

For the CGI-I, we anticipate a positive response rate of 50% to 60% to SPT versus 30% to 40% in the SPE group, based on our prior PT study (Bearss et al., 2015). By convention, participants who drop out are included in the negative treatment response group. The sample size of 130 participants provides at least 80% power to detect a 20% difference on the CGI-I (e.g., 50% SPT versus 30% SPE); chi square = 5.2 (p=0.022), odds ratio =2.19.

Analytic Plan for Aim 1a. The primary outcome is the parent-rated PAIRS, a newly validated, continuous measure assessing insomnia severity in children with ASD. It will be collected at

baseline, midpoint (Week 5) and endpoint (Week 10) in the randomized phase. Longitudinal differences in PAIRS between randomized groups will be tested for significance using a general linear mixed effects regression model (GLMM). Randomization group, study time, and group by study time interaction will be treated as fixed effects. Random effects will be intercepts for repeated PAIRS measures nested within participants and participants nested within study sites, as appropriate. If study site is statistically insignificant as a random effect, site will be included as a fixed effect. The GLMM will use data from all study time points and report on the baseline-adjusted least-squares mean (LS-mean) difference in PAIRS at Week 10 for SPT compared to SPE, with 95% confidence interval (CI) and p-value. In addition to the Week 10 baseline-adjusted LS-mean difference, we will report a Cohen's *d* effect size, calculated by dividing the Week 10 LS-mean difference in PAIRS by the pooled standard deviation at baseline for the entire study sample, to assist in the interpretation of a minimum clinically important difference (MCID) noted above. Cohen's *d* effect sizes will be interpreted as small (0.2), moderate (0.5), and large (0.8).

Aim 1b. Our prespecified secondary measure is the rate of positive response on the CGI-I, defined as Much Improved or Very Much Improved, rated by a treatment blind Independent Evaluator (IE). Inputs to the CGI-I will include child-specific Parent Target Problems, changes on the PAIRS and Aberrant Behavior Checklist (Irritability and Hyperactivity subscales) at study follow-up time points. The CGI-I will be tested for a difference in the proportion of positive response at study endpoint (Week 10) between groups using a chi-square test of independence. We have used this approach in several previous behavioral intervention trials in young children with ASD (Bearss et al., 2015; Johnson et al., 2023; Scahill et al., 2022).

Exploratory Analyses

Exploratory Aim 1: The Parental Distress subscale of the Parenting Stress Index (PSI) is a pre-specified outcome in the PSI because the content of this subscale measures parental distress due to the difficulties of managing the child's disruptive behavior. This measure will be collected at baseline and Week 10 in the randomization phase to evaluate the impact of SPT on parental well-being compared to SPE using the same GLMM described above. Based on prior studies, we will conduct additional exploratory analyses on the PSI Difficult Child and the Parent-Child Interaction subscales (Johnson et al. 2023; Postorino et al. 2019).

Exploratory Aim 2*:* To evaluate the stability of treatment effect post-treatment, GLMM and generalized regression methods will be used to analyze outcome data collected at Week 20 for the **SPT group only**. Specifically, for PAIRS, results will compare the LS-mean estimate at Week 20 versus Week 10 for statistical significance; for CGI-I, an odds ratio for response at Week 20 relative to Week 10 will be calculated. We will also look at the trajectory from baseline to midpoint, endpoint and Week 20.

Exploratory Aim 3: To test for effect modification in the association between randomized treatment groups and the CGI-I outcome at Week 10, a battery of candidate potential effect-modifying measures will be evaluated, including, anxiety (Parent-Rated Anxiety Scale–ASD), behavioral rigidity (Behavior Inflexibility Scale), sensory sensitivity (Short Sensory Profile), disruptive behaviors (Aberrant Behavior Checklist–Irritability and ABC–Hyperactivity), adaptive behavior (Vineland Daily Living and Adaptive Behavior Composite) and PSOC categories described below. Continuous candidate effect-modifying measures will be categorized using specific cut points (e.g., median, ≥75th percentile) to facilitate interpretation. Effect modification will be formally assessed by including interaction terms between randomized treatment group and each candidate effect-modifying measure in regression models for the CGI-I outcome. A

significant interaction term will indicate that the association between treatment and outcome differs across levels of the effect-modifying measure.

Parent Sense of Competence (PSOC) Scale is a special case. At baseline, we will classify children based on 9 reverse scored items rated Somewhat Disagree and Strongly Disagree and 8 non-reversed scored items Somewhat Agree and Strongly Agree (positive PSOC indicator) vs Somewhat Agree and Strongly Agree on reverse scored items Somewhat Disagree and Strongly Disagree and 8 non-reversed scored items (negative PSOC indicator) in SPT and SPE. Does classification in the *positive* PSOC group on Satisfaction or Efficacy subscales vs negative PSOC moderate treatment response.
Exploratory Outcome Analysis: Compare the rates of *positive* and *negative* PSOC indicators in SPT and SPE at baseline and Week 10. Compare rates of conversion from negative to positive in SPT vs SPE. Exploratory- treat PSOC as a continuous measure (Iadarola et al. 2018).

Exploratory Aim 4 (Exploratory Moderators**):** Other moderators of treatment response such as socioeconomic level, caregiver education, and number of adult caregivers involved in the child's bedtime/nighttime care. Testing the impact of these demographic and situational moderators may provide important information on the management of insomnia symptoms in young autistic children.

Adverse events Adverse events (AEs) that occur after random assignment, whether presumed related to treatment or not, will be documented as an AE and rated as Mild, Moderate or Severe. The occurrence of an AE will be counted once at the highest level of severity (e.g., a report of mild nausea followed by a report of moderate nausea in the same child would be counted as an occurrence of moderate nausea). The frequency of AEs by treatment group will be evaluated with Fisher's exact test.

Management of Missing Data. Our missing data plan includes inquiries about the reasons for missing data or attrition. The pattern of missing data and rate of attrition will be examined and reasons documented. We will handle missing data in several ways (Kenward and Carpenter, 2007). First, missing data for certain child covariates will be imputed by carrying forward or backward information nearest to the missing encounter, when clinically justifiable.
Second, any residual missing baseline covariates (e.g., demographic factors) will be analyzed as observed; if baseline missingness is substantial or considered to be a source bias, multiple imputation will be performed as a sensitivity analysis (10 imputations). For any analyses incorporating imputed baseline covariates, estimates and standard errors will be pooled across imputed datasets using Rubin's rules. Third, for longitudinal outcomes, mixed-effects models will be estimated using full information maximum likelihood (FIML), which will incorporate all available data under the assumption that missing data are missing at random (MAR) and will avoid listwise deletion. To evaluate the MAR assumption, baseline characteristics of participants with substantial missing data will be compared to those who complete the study, and differences in attrition by treatment group (SPT versus SPE) will be assessed. If missingness differs across groups in ways not explained by observed variables, secondary sensitivity analyses using pattern-mixture models will be conducted. For the CGI-I, participants with missing follow-up data will be classified as non-responders (Bearss et al., 2015; Scahill et al., 2022).

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