Protocol Title: Telehealth Delivery of Treatment for Sleep Disturbances in Young Children with Autism Spectrum Disorder

Funding: Department of Defense

Principal Investigator: Cynthia Johnson, PhD

Background

ASD is a Major Health Problem in Need of Evidenced-Based Treatments.

Current estimates of the prevalence of ASD range from 6.2 to 14.7 per 1000.[1,2] In addition to the core features of ASD (social communication deficits; repetitive and restrictive behaviors), as many as 70% of children with ASD have additional problems such as hyperactivity, disruptive behavior, and anxiety severe enough to warrant treatment.[3-8] An estimated 44 to 80% of children with ASD also have sleep disturbances.[9-12] This wide range reflects differences in the source of sample, assessment methods and severity level (mild to severe). The estimate of 80% likely includes children with mild sleep disturbance. Children with ASD and moderate or greater levels of severity require intervention.[13] Providing appropriate treatment for children with ASD is a challenge to the service system, with current costs estimated to be $125 billion annually.[14] Treatment approaches commonly used for core and associated features include behavior therapy,[15-17] comprehensive educational interventions[18,19] and pharmacotherapy.[20,21] The heightened recognition and increased demand for services, however, occurs against a backdrop of insufficient evidence for many treatments.[22-25] There is a pressing need to conduct well-designed studies to expand the portfolio of ***empirically supported, time-limited and cost-effective interventions*** to meet rising demand and guide clinical practice.[26]

According to the World Health Organization, a major obstacle for access to adequate services for children with disabilities is the lack of trained specialists.[27] Although children with ASD account for 10–14% of those referred for mental health treatment, only 5% of mental health practitioners consider themselves prepared to treat children with ASD.[28] Moreover, training in behavioral health programs on the assessment and treatment of pediatric sleep disturbances is limited.[29] As a result, the demand for treatment of children with ASD and sleep disturbances far outpaces the availability of empirically supported interventions and skilled providers in the community. This lack of access often results in long waiting lists for services and families resorting to treatments without empirical support.[30] In a randomized trial of 180 young children with ASD, we showed that parent training was superior to parent education for reducing disruptive behavior.[31] This project will test whether telehealth delivered parent training for sleep problems is superior to parent education in children with ASD.

Importance of Sleep.

Biological and environmental factors play a role in the development and maintenance/disruption of the sleep-wake cycle. The hypothalamus controls the timing of sleep, body temperature and cortisol production. Melatonin (produced by the pineal gland) affects sleep-wake patterns via feedback between the pineal gland and hypothalamus. This hormone is suppressed by exposure to bright light. Factors such as light perception, social cues, ambient temperature, noise levels, and internal body signals (hunger, body temperature) also contribute to the sleep-wake rhythm.[32] Sleep requirements vary by age: children 2 to 5 years require 11-13 hours of sleep per day; school-age children require 10-11 hours.[33-37]

Over fifty years of research attest to the critical need for adequate sleep. Sleep plays a central role in early brain maturation [38-40] and plasticity.[41-47] Inadequate sleep in school-age children can impair cognitive functions such as working memory and abstract thinking,[48-51] motor reaction time;[52] attention,[45,48,51,53-59] emotion regulation[48,51,60-62] and academic functioning.[54,57,63,64] Although limited, available evidence suggests a clear link between disrupted sleep and daytime behavior problems in young children.[62,63,65] Sleep disturbances in young children may also have adverse effects on family functioning due to parental sleep deprivation.[66-68]

Sleep, Mental Health & Physical Health.

Sleep disturbances are associated with several mental health disorders including anxiety, depression, attention deficit hyperactivity disorder (ADHD), post-traumatic stress, and bipolar disorder.[69-75] Several studies show the common co-occurrence of sleep problems and emotional problems in children.[74,76,77] Emerging data link sleep disruption to the *onset* of internalizing and externalizing problems in children.[60,78,79] These findings have prompted a shift in treatment paradigms to address sleep difficulties alongside the emotional and behavioral problems or even as a first step in the treatment plan.[75,80-82] Moreover, there are physical health implications for

chronic, inadequate sleep and poor sleep quality.[83-85] ***Collectively, there is compelling evidence that intervening early on sleep disturbances in young children with ASD could offset a range of untoward events and maximize a child's participation in early therapeutic and educational activities.***

Sleep Disturbances in Children with ASD.

The prevalence of sleep problems in the general pediatric population is estimated at 25%.[86] By contrast, poorly regulated sleep patterns (trouble falling asleep, mid-sleep awakening and early morning awakening) affect as many as 80% of children with ASD regardless of cognitive functioning level.[10,11,67,87-98] Although severity of sleep dysregulation in children with ASD varies from mild to severe, children with moderate or greater sleep problems require treatment to avert the associated adverse effects of inadequate sleep. Closely related problems for children with ASD include noncompliance with bedtime routines, difficulty establishing essential elements of sleep hygiene due to over-arousal and sleep-onset association problems (e.g., only able to fall asleep somewhere other than bed, requires certain objects or person to be present for sleep onset),[12] resulting in overall lower sleep quality.[99]

Johnson[10] long ago proposed that the core social communication deficits of ASD, and often co-occurring cognitive deficits, interfere with the child's capacity for self-soothing. Consequently, children with ASD may be less able to promote *sleep onset* independently or return to sleep upon waking after sleep onset.[10] Children with ASD may also have difficulty understanding social and environmental cues that are part of the *bedtime routine.* Some children with ASD develop idiosyncratic bedtime routines that hinder sleep such as insisting on toys be arranged just so with attendant disruptive behavior that interferes with settling down.[99] Co-occurring gastrointestinal problems, seizures, anxiety, depression, ADHD, or medication side-effects (e.g., stimulants, serotonin reuptake inhibitors) may also interfere with sleep patterns.[90,100-106] Alteration in melatonin secretion in children with ASD may contribute to sleep disturbance.[107,108] Several studies have reported markedly lower mean plasma melatonin levels and lower urinary excretion of melatonin sulfate (MEL-S, also known as 6-MEL-S) in ASD compared to typically developing controls.[109-111] In sum, disruptive behavior, elaborate bedtime routines, poor self-soothing and understanding of environmental cues, neurochemical alterations, and concurrent medical problems may interfere with developing a stable sleep-wake cycle in children with ASD.

Disordered sleep in children with ASD can amplify already delayed social interactions, repetitive behaviors, affective problems, inattention/hyperactivity, and irritability.[88,112-117] Given the documented detrimental effects of sleep disturbance on cognition, attention, memory consolidation, and daytime behavioral adjustment, addressing sleep disturbances in young children with ASD may promote overall improvement and fuller use of educational and therapeutic interventions. Sleep difficulties in children with ASD produce significant stress on caregivers and negative attitudes toward the child.[88,118-120] Parents of children with ASD have poorer sleep quality than parents of typically developing children.[121,122] Sleep problems in the child may contribute to lower quality of sleep in mothers,[123] and are inversely correlated with maternal depressive symptoms.[124] Interventions that improve sleep in the child may reduce parental stress and improve mood and overall health.

Interventions for Sleep Disturbance in Children with ASD.

Supplemental melatonin, which is safe and inexpensive, has shown promise as a treatment for sleep onset delay in children with ASD.[32,109,125-133] However, melatonin does not address behavioral bedtime resistance, teach self-soothing to promote sleep, and may not be helpful for night wakings.[109,133] Not surprisingly, behavioral interventions for sleep disturbances remain first line treatments for insomnia in general pediatrics.[134,135] However, behavioral interventions for sleep disturbances in children with ASD have not been carefully studied. Ironically, surveys indicate that most parents of children with ASD favor behavioral approaches over sleep-enhancing medications.[120] Based on successful behavioral interventions for sleep onset and maintenance problems used in typically developing children, similar approaches have been used clinically in children with ASD with some success.[96,135] Specific adaptations for children with ASD and other developmental disorders include establishment of routines, environmental modifications, placing sleep restrictions on the child, extinction procedures, and scheduled awakenings.[136-146] The time is right to pursue a well designed randomized trial targeting sleep disturbances in children with ASD to guide clinical practice with the goal of optimizing the reach of the intervention via telehealth.

Behavioral Parent Training in ASD.

Parents confront daily struggles in rearing a child with ASD. Sleep disturbances present yet another challenge. Parent training (PT) is a fitting treatment model for sleep problems in young children with ASD for several reasons: 1) the central role of parents in promoting the development of children with ASD; 2) the demonstrated feasibility of parent training in the treatment of sleep problems (see below); and 3) the negative impact of sleep disturbances on the child and family. To date, structured PT interventions have focused largely on child language, adaptive skills, joint attention and other social communication behaviors.[147-150] There is a growing body of empirical support for the efficacy of PT in children with ASD and disruptive behavior.[31,149-153] In two previous large-scale multi-site trials, we showed that PT was effective for reducing disruptive behavioral problems and improving daily living skills compared to parent education.[31,154] Our PT program included one session on sleep problems, which was helpful for some children. For children with ASD and moderate to severe sleep problems, however, more intensive and focused treatment on sleep may be required.

In a review of 24 published studies on behavioral interventions that targeted sleep problems in children with ASD and other developmental disabilities, most studies were small case series or single subject design studies. These studies set the stage for a large RCT as the next step in keeping with the recommendations of an NIMH convened workgroup.[155] To date, there have been only two large-scale RCTs of a behavioral intervention for sleep disturbances in children with ASD.[143] Cortesi and colleagues[156] compared the efficacy of 4 sessions of PT to PT plus melatonin (MLT), MLT alone and placebo in a sample of 160 4-10 year-olds with ASD. After 12 weeks, all three active treatments showed superiority to placebo in sleep onset latency (SOL) and wakings after sleep onset on actigraphy and a parent completed questionnaire. There was a statistical *trend* favoring combined treatment. In a randomized sample of 80 children with ASD, ages 2-10 years with sleep onset problems, Malow and colleagues compared a single parent individual educational session to two group sessions. Both programs showed improvement in SOL and modest improvement in sleep efficiency on actigraph.[157] Although these studies expand the evidence-base on sleep interventions for children with ASD, both have notable limitations. The four-group study by Cortesi et al.[156] excluded children with behavioral problems, which limits generalizability. In addition, subjects whose treatment compliance fell below 80% (n=16) were excluded from the analysis. The Malow et al. study was brief and focused primarily on sleep latency. These studies were all delivered in a tertiary clinical setting. These settings are limited to their access to families who may have to travel distances and may have long waiting lists.

Although prior research documents the high rate of moderate or greater sleep problems in children with ASD and the potentially detrimental effects, available evidence on intervention is encouraging but inconclusive. **The time is right for an innovative telehealth trial of an exportable parent training intervention for sleep disturbances in young children with ASD.** In a prior pilot study (R34MH082882 – PI Johnson[97]), we showed that our SPT for young children with ASD and sleep disturbances was acceptable to parents and reliably delivered by therapists (see Support section for reference of the published paper of this pilot trial). We now propose a RCT to test the efficacy of telehealth delivered SPT against parent education – which will control for time and attention.

Telehealth and ASD

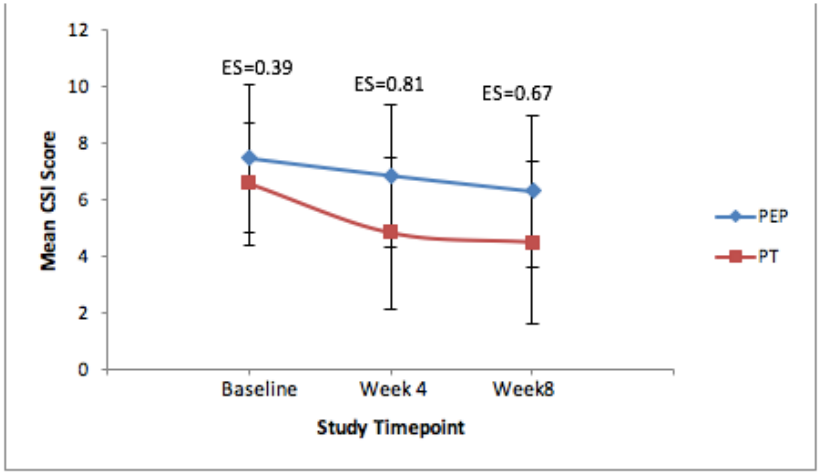
Telehealth, also referred to as telemedicine and more recently telepractice, is the use of communication technologies to allow delivery of services across a range of conditions and over geographical distances.[158] The capacity of telehealth to deliver empirically based interventions for children with ASD holds promise as a means to close the gap between demand for services and the availability of autism specialist in underserved and rural areas such as those making up large swaths of the state of Florida. Despite the potential for telehealth in the delivery of assessment and treatment of children with ASD, this has received limited research attention. A few studies have demonstrated the use of telehealth to delivery interventions that are acceptable to parents but this is a under developed area at present.[159-163] Treatment for sleep is particularly suited for telehealth as this allows for more ecologically sound delivery of the intervention close to bedtime.

Preliminary Data

Do previous findings suggest SPT for sleep disturbances in children ASD can be effective?

In our prior NIH-funded pilot study (R34MH082882; Johnson, Turner, Foldes, Brooks, Kronk, Wiggs [97]), we showed that our structured 5 session parent training intervention for young children with ASD and sleep disturbances was acceptable to parents and reliably delivered by therapists in a clinic setting. Parents attended 97% of expected sessions; parent satisfaction was high. Treatment fidelity (therapist integrity and parent adherence) was over 95%. The SPT group improved significantly more than the comparison group based on the primary outcome of the CSI of the MSPSQ (see Figure 2).[97] Using a benchmark of ≥30% improvement on the CSI, the SPT group had a positive response rate of 60% compared to the PE group (33%). Again, this study was delivered in a tertiary, specialized setting requiring parents to make many trips to an urban area; some families traveled over two hours to participate.

Figure 1. Mean CSI Scores with Effect Sizes



What was learned from our previous study?

A number of lessons were learned from this earlier study which will benefit this current project. First, telehealth SPT will be delivered over 10 weeks (versus 8 weeks in the previous study). This provides more time for parental application of strategies in the home and more time to detect change. Second, the time and distance was a barrier for potential participants who would have otherwise met eligibility criteria.

What is the impact of child sleep disturbance on parents?

In 49 children (mean = 3.48± 1.02 years) with ASD and their parents, the CSI was highly correlated with a measure of parent sleep quality (Pittsburgh Sleep Quality Index) (r=.52; p <.001). As sleep disturbances in children increased, parents' sleep worsened.[164]

Experience with the use of telehealth platforms?

Dr. Johnson and colleagues are currently conducting an NIH-funded multi-site pilot study of a behaviorally-based parent training program targeting feeding problems in young children with ASD. The study utilizes a HIPAA-compliant teleconferencing system (VSEE) to provide clinic-to-home parent-child coaching during mealtimes even though the parent training sessions per se are provided in a clinic setting. All families randomized to treatment thus far (N=22) have been able to successfully connect through the system in order to receive in-vivo coaching from a therapist during mealtimes. In conducting this trial, the idea to use a telehealth platform in the delivery of SPT was generated. The use of a telehealth platform has particular advantages to address sleep disturbances. Aside from the advantage of reaching families who may be a distance from a university setting, the use of the platform allows more flexibility in scheduling to include scheduling in the evening around bedtime, allows for real-time parent-child coaching soon after learning about the procedures discussed, and overall greatly enhances the ecological validity of the intervention.

For this trial, the telehealth platform will be the Cleveland Clinic Express Care Online. This platform is also HIPAA-compliant, and has capabilities that are similar to VSEE.

Objectives / Specific Aims / Hypotheses

Across a range from mild to severe, as many as 80% of children with autism spectrum disorder (ASD) have sleep disturbances.[9,12,94,97,165] Sleep problems in typically developing children have adverse impacts on daytime behavior, emotion regulation, learning, physical health, as well as parent and family functioning.[52,84,123,166,167] For children with ASD whose development is compromised by a range of deficits, the impact of sleep disturbances may be more far reaching. Given the improved recognition of ASD and the prevalence of sleep disturbances in this pediatric population, increased demand for treatment of children with ASD and sleep disturbances in pediatric sleep clinics, community behavioral health clinics and specialized ASD programs is inevitable. Accumulating data indicate that behaviorally based interventions for sleep disturbance can be effective. Despite the recommendation for these interventions in pediatrics broadly[168] and ASD specifically, there have been few randomized controlled trials of behavioral interventions for sleep disturbance in children with ASD and none of these small trials included telehealth.

In response to **FY17 ARP Clinical Trial Award funding opportunity (W81XWH-17-ARP-CTA),** this four-year study will test the efficacy of a behavioral parent training intervention specifically designed for sleep disturbances and delivered individually through the HIPAA compliant Cleveland Clinic Express Care Online telehealth platform. **This study will address the following areas of interest: 1) Behavioral, cognitive and other non-pharmacological therapies and 2) Therapies to alleviate conditions co-occurring in ASD (e.g, sleep disturbances).**

A sample of 90 children with ASD (ages 2 to less than 7 years) and moderate or greater sleep disturbances will be **randomly** assigned to 10 weeks of a structured, 5 session sleep parent training (SPT) program or 10 weeks of a structured, 5 session parent education (SPE) program. Our recently completed randomized pilot trial (n=33) demonstrated that SPT is acceptable to parents and provided promising preliminary efficacy data.[97] We now propose an efficacy study of SPT delivered individually via telehealth platform for sleep disturbances in young children with ASD. We will also examine the impact of SPT on the child's overall functioning and parental quality of life. Children who do not show a positive response to SPE will be offered SPT at no charge by study therapists.

Primary Aim

To evaluate the efficacy of telehealth deliver of SPT (n=45) compared to telehealth delivery of SPE (n=45) for sleep disturbance in children with ASD.

Hypothesis 1: After 10 weeks of treatment, children whose parents receive SPT will show greater improvement in sleep as evidenced by reduction on the Composite Sleep Index (CSI) of the modified Simonds and Parraga Sleep Questionnaire[97,144] compared to children whose parents receive SPE.

Hypothesis 2: After 10 weeks of treatment, children whose parents receive SPT will show a significantly higher rate of overall improvement on the Improvement scale of the Clinical Global Impression (CGI-I), as assessed by an independent evaluator masked to group assignment, compared to children whose parents receive SPE. Ratings of Much Improved or Very Much Improved will be used to define positive response.

Hypothesis 3: After 10 weeks of treatment, children whose parents receive SPT will show significantly reduced disruptive behavior on the parent-rated Irritability subscale of the Aberrant Behavior Checklist (ABC) compared to children whose parents receive SPE.

Hypothesis 4: At post-treatment follow up on Week 16, children in the SPT group will continue to show significantly lower scores on the CSI and a significantly higher rate of positive response on the CGI-I scored by an Independent Evaluator masked to treatment assignment compared to children in SPE.

Secondary Aim

To evaluate the impact of SPT on parental quality of life (parental stress, parental competency, mental health and sleep quality) compared to SPE.

Hypothesis 1: After 10 weeks of treatment, parents enrolled in SPT will report lower levels of stress and higher levels of competency and health as measured by the Parenting Stress Index (PSI), Parenting Sense of Competence (PSOC), and Parent Health Questionnaire (PHQ) compared to parents in SPE.
Hypothesis 2: After 10 weeks of treatment, parents receiving SPT will report improved sleep for themselves on the Pittsburgh Sleep Quality Index (PSQI) compared to parents receiving SPE.

Study Design

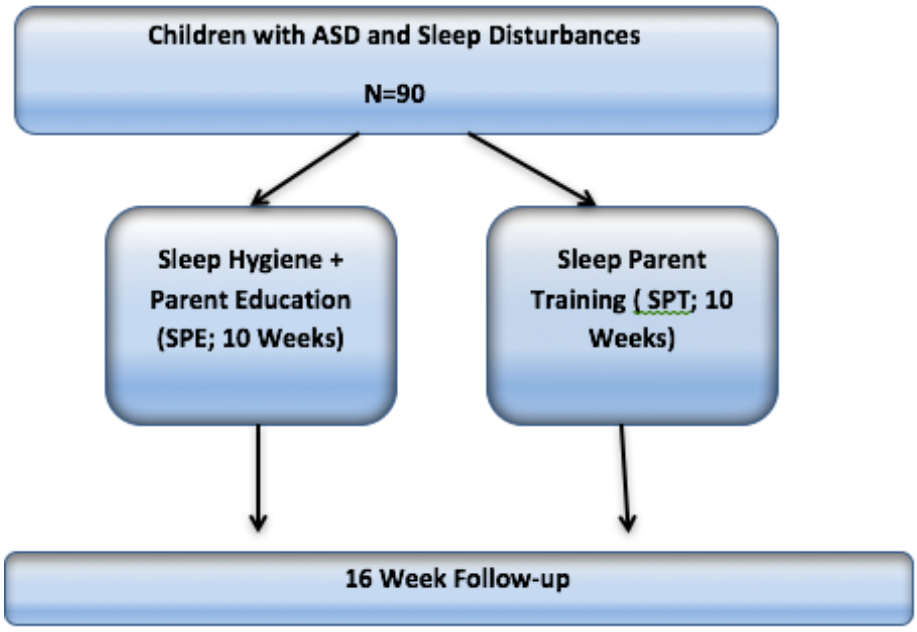
As shown in Figure 2, 90 eligible subjects will be randomly assigned in a 1:1 ratio to sleep parent training (SPT) or sleep parent education (SPE) using a randomized block design (random blocks of sizes 4 and 8), with allocation concealed to investigators. Both treatments provide 5 individually-delivered sessions over 10 weeks. All participants will be assessed on study outcomes at Weeks 5 and 10 as well as 6 weeks post-treatment. *Parents who complete SPE may receive SPT **after** the Week 16 evaluation*.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Both genders ≥2 and ≤7 years of age [RATIONALE: Based on pilot findings with similar age range[97]]
2. Clinical diagnosis of ASD corroborated by the Modified Checklist for Autism in Toddlers[169] or the Social Communication Questionnaire.[170] We will collect the MCHAT on children 2-3 years of age, both MCHAT and SCQ on children >3-<6, and SCQ for children >6-7 years of age via REDCap (Research Electronic Data Capture,[171] see details in the Data Management section). We will use recommended cutoff scores (score of 8 for MCHAT and 15 for SCQ) for inclusion.
3. Score of ≥5 on the CSI and a Clinical Global Impression Severity (CGI-S) score of Moderate or greater. [RATIONALE: This CSI score reflects moderate sleep disturbances and was the entry score in prior studies by Johnson et al[97] and Wiggs and Stores;[144] The CGI-S score of Moderate is commonly used as clinician validation of parent ratings.]
4. Medication and supplement free or on stable medication or supplements (no changes in the past 6 weeks and no planned changes for 16 weeks). [RATIONALE: Many children with ASD are on medication for various target behaviors that may affect sleep. Children on stable medication (or supplement) for sleep, who otherwise meet study entry criteria, will be included because residual sleep problems remain. Including children on stable medication (or supplement) will enhance the representativeness of the study sample.]

Figure 2



5. Parental proficiency in spoken and written English language. [RATIONALE: At the present time, study materials and many of the study measures are available only in English. If SPT is efficacious, we will take the next steps to translate the manual].

Exclusion Criteria

1. Children with a serious medical condition or a known or suspected medical cause for sleep disturbances (e.g., nocturnal seizures, unresolved gastrointestinal problems such as reflux or constipation).
2. Children with a psychiatric disorder or serious behavioral problems requiring immediate treatment.

3. Children with known or suspected sleep apnea, restless legs, or periodic limb movements during sleep, or a circadian-based sleep disorder (e.g. delayed or advanced sleep phase syndrome) based on history and all available information. [RATIONALE: Children with these conditions warrant a different treatment. We will provide referrals as needed.]

Recruitment

To randomize 90 subjects, we expect to screen approximately 120 subjects. Approved advertisements about the project will be circulated within the Cleveland Clinic Center for Autism and other key programs within the Cleveland Clinic systems. Regional autism programs in the community will also be approached and provided information about the study. In the state of Florida, the university-based Centers for Autism and Related Disabilities (CARDS), with whom the PI has relationships, have over 3000 children registered in this young age range. The study will also be posted on ClinicalTrials.com. With distance not a limiting factor with telehealth delivery, recruitment is anticipated to be easily attainable.

Study Procedures and Randomization

Visit Schedule for Assessments

Screening Visit:

Subjects who appear to be eligible on a telephone interview will be scheduled for an Express Care Online screening visit. After obtaining informed consent which the family will access and sign using a REDCap link, parents will completed the assessment measures to confirm eligibility (see Table 1).

Baseline Visit:

Once eligibility is confirmed, an Express Care Online baseline visit will occur within 7-14 days of screening to complete additional measures (see Table 1). Parents will also be instructed to take photographs of their child's sleep environment for review and treatment planning during the baseline visit.

Randomization:

Participants will be randomly assigned to SPT or SPE at the conclusion of the baseline visit in a 1:1 ratio. A randomized block design (with random blocks of size 4 and 8) will be used to ensure balance as well as maintaining the blinding of allocation assignment by investigators. The randomization module in REDCap will be utilized to reveal the assignment for each participant. Assignment status will be maintained in a separate REDCap data set, with a shared identifier to be able to link to the study database for final analysis. Limited study staff who are not masked to treatment group assignment will have access to this database.

Post-randomization Assessments:

Assessments for both groups will be repeated at Weeks 5, 10 and 16 (see Table 1). The classification of positive or negative response will be made at Week 10 (endpoint of the randomized trial). To protect the treatment blind for IEs and to assess the effects of time within each treatment, all subjects will be asked to return at Week 16.

Establishing Study Inclusion Criteria, & Subject Characterization

Developmental, Medical, & Sleep History.

This questionnaire will be completed by the parent / caregiver at screening to document prenatal, perinatal or postnatal medical and developmental histories including, sleep, medication and past assessments (see Survey and Questionnaires section). If any questions arise that would exclude the child and/or warrant other care, we will discuss with the family. This history form requires 20-30 minutes to complete.

The Modified Checklist for Autism in Toddlers (M-CHAT-R)[169] is a 20 items screening measure to detect high risk toddlers for ASD. This measure has been well validated and widely used. Scores between 8-20 are in the high risk range. We will use a score of $\geq$8 to corroborate the clinical diagnosis required for CARD registration. Internal consistency across all of the M-CHAT-R items fell below the adequate threshold (Cronbach's alpha = 0.63); however, when the second stage of the M-CHAT-R was examined internal consistency was found to be adequate (Cronbach's alpha = 0.79). The M-CHAT-R initial scoring, with a cutoff score of 3, has a sensitivity of 0.911, and specificity of 0.955, both with a 95% CI. [169] M-CHAT requires 10-15 minutes to complete and is written on 4th grade reading level.

The Social Communication Questionnaire (SCQ)[170] is a parent report screening measure for autism spectrum

disorders (ASD) based on the Autism Diagnostic Interview-Revised (ADI-R) algorithm items. It has 40 yes and no questions centered around core features of ASD, and can be complete in 10-15 minutes. The SCQ shows high discriminative validity between ASD and non ASD populations, similar to the much lengthier ADI-R. ROC analyses established a cutoff score of 15 on the SCQ to differentiate between ASDs and other diagnoses. At this cutoff score, sensitivity was .85 and specificity was .75. The alpha index of internal consistency was uniform across diagnostic groups, ranging from .84 to .93. A cut off score of ≥15 will be used to corroborate a clinical diagnosis and used for inclusion. The SCQ requires 10 minutes to complete and written on 4th grade reading level.

Clinical Global Impression-Severity (CGI-S)[172]

This 7-point scale ranges from 1 (*Normal*) through 4 (*Moderate*) to 7 (*Extreme*). Although sleep problems will be given particular weight, independent evaluators will consider all aspects of the child's condition to assign the CGI-S score. A score of ≥ 4 (Moderate) is required for entry.

Table 1. Schedule of Measures	Screen	Baseline	Wk 5	Wk 10	Wk 16
Parent Completed Measures					
Demographics, Medical & Developmental History	X				
Modified Checklist for Autism in Toddlers **or** Social Communication Questionnaire	X				
Composite Sleep Index (CSI)	X	X	X	X	X
Aberrant Behavior Checklist (ABC)		X	X	X	
Parent Stress Index (PSI)		X	X	X	
Parenting Sense of Competence Scale (PSOC)		X	X	X	
Parent Health Questionnaire (PHQ)		X	X	X	
Pittsburgh Sleep Quality Index (PSQI)		X	X	X	
Clinician Ratings					
Clinical Global Impressions - Severity		X	X	X	
Clinical Global Impressions –Improvement (CGI-I)		X	X	X	X
Safety Review	X	X	X	X	X
Therapist Measures					
Treatment Fidelity Checklists	Completed at each session				

Outcome Measures

Sleep Measure

Composite Sleep Index (CSI) from the MSPSQ[97,144,173]

The CSI is a 6-item parent-report measure where items are rated 0 to 2 (range 0 to 12) with higher scores reflecting greater sleep problems. Thus, *change in an item score of 1 or 2 points reflects a clinically relevant change*. For example, for the question on frequency of night wakings, a reduction from 2 to 1 point would reflect improvement in night wakings from every night to one-two nights per week; a reduction to 0 would reflect an improvement to once a month or less. The reliability and validity of the CSI has been established as a nested scale within the MSPSQ.[174] Thus, we will use the full MSPSQ. Wiggs and Stores[175] reported the test-retest reliabilities for a 2 week period to be .83 to 1.0. In a larger study of 345 individuals with intellectual disability, Maas et al[176] found the internal consistency of the items of the MSPSQ to be good (Cronbach's α = .80). Maas et al[176] also evaluated the convergent validity of the MSPSQ with a similar measure, the Sleep Disturbance Scale for Children (SDSC) and found a correlation (r = .79, p<.001) showing adequate validity. The MSPSQ has been reported to be acceptable to parents.[175] This measure can be completed within 5-10

minutes and is at a 5th grade reading level.

Child Behavior Measures

Improvement scale of the Clinical Global Impression (CGI-I)[172]

This is a clinician-rated, 7-point scale designed to measure overall improvement from baseline. Scores range from 1 (Very Much Improved) to 4 (Unchanged) to 7 (Very Much Worse). An independent evaluator (IE) **blinded** to group assignment will use all available information to judge treatment response. By convention, CGI-I ratings of Much Improved (score of 2) or Very Much Improved (score of 1) are used to classify subjects as positive responders. All other scores classify subjects as negative responders. An essential contributor to the CGI-I is the content of the semi-structured Parent Target Problem interview.[31] At baseline, the IE asks the parent to nominate the child's two most important problems. Based on the study entry criteria, we expect that one problem will be sleep related. The parent will also be asked to identify a second problem. Through brief discussion, the frequency (for episodic behaviors such as night wakings) or constancy (hyperactivity) reflecting more enduring patterns, intensity and impact of the behavior on the family are established. Responses from this systematic inquiry are documented in a brief narrative. The narrative will be reviewed and revised at Weeks 5, 10 and 16. This method has been shown to be reliable and valid in a previous parent training study[31,177] and currently being used in our RCT on parent training for feeding problems.

Aberrant Behavior Checklist.[178,179]

This is a reliable and valid 58-item parent-report questionnaire with five subscales: Irritability (agitation, aggression and self-injurious behaviors), Social Withdrawal, Stereotyped Behaviors, Hyperactivity, and Inappropriate Speech. The ABC has shown adequate sensitivity to change in several pharmacological and behavioral treatment studies.[148,180-183] The revised ABC manual[184] cites 35 scientific papers that support the convergent validity of the ABC, and its concurrent validity with several established instruments regularly used in intellectually and developmentally disabled populations. Each item is rated on a Likert scale from 0 (not a problem) to 3 (severe in degree). For the current study, we are primarily interested in change of the Irritability and Hyperactivity subscales as a proxy for sleep-related impairment (i.e., daytime behaviors secondary to sleep disturbances). Requiring an 8th grade reading level, this measure requires 15-20 minutes to complete.

Quality of Life Measures

Parenting Stress Index-Short Form (PSI)[185]

This is a 36-item parent-completed questionnaire for children 12 years of age and younger and has three scales: 1) Parental Distress; 2) Difficult Child Characteristics; and, 3) Dysfunctional Parent-Child Interaction. This measure was developed from the Parenting Stress Index Full Form using factor analysis, and has been used to assess parental stress and parent-child relationships in children with autism and intellectual disabilities.[185-189] The PSI has good test-retest reliability with an average score of .76 (min= .68, max= .85), and internal consistency (Cronbach's alpha average of .85, min= .8, max=.91). A total score of 88 (85th percentile) and above is considered in the clinically significant range for parental stress. The PSI has good convergent and concurrent validity across clinical and nonclinical samples, and diverse populations. We confirmed the factor structure in a recent study.[190] We have used this for several other trials and it has been shown to be sensitive to change in parent training studies.[191] This measure may be completed within 10-20 minutes and written at a 3rd grade reading level.

Parent Health Questionnaire-4 (PHQ-4)[192]

This brief self-report is designed to assess parental mental health. It has been shown to be an effective screen for anxiety and depression disorders. Requiring 5 minutes to completed and written at 5th grade reading level.

The Parenting Sense of Competence scale (PSOC)[193]

This 17-item scale was developed to assess parental self-efficacy. Each item is answered on a 6-point scale ranging from strongly disagree to strongly agree. The measure has high internal consistency and solid test-retest reliability. The Satisfaction subscale measures parental motivation and frustration (e.g., "Even though being a parent could be rewarding, I am frustrated now while my child is at his/her present age"). The Efficacy subscale measures perceived self-efficacy to change the child's behavior (e.g., "I meet my own personal expectations for expertise in caring for my child"). The PSOC also yields a Total Competence score, with

higher scores reflecting higher competence. In a community sample of mothers,[194] subscale total scores of Satisfaction (22.72) and Efficacy (22.03) were reported. We have used this measure in another study of parent training and it has been shown to be sensitive to change.[195] This measure is written at an 8th grade reading level and requires approximately 15 minutes to complete.

Pittsburgh Sleep Quality Index (PSQI)[196]

This 19-item, self-rated questionnaire will be completed by parents. It is used in adult sleep medicine research as a reliable measure of sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime functioning. Overall, it has a reliability coefficient (Cronbach's alpha) of 0.83, indicating a high degree of internal consistency. For the subgroup that was tested at two time points, the correlation coefficient for global PSQI scores was 0.85 ($p<0.001$). Distribution of global PSQI scores differed between groups. A cutoff score of 5 correctly identified 88.5% of all patients and controls (kappa=0.75, $p<0.001$). This represents a sensitivity of 89.6% and a specificity of 86.5%. PSQI estimates of sleep variables were compared to polysomnographic findings. T-tests showed no differences between PSQI sleep latency estimates and those found using polysomnography, but estimates of usual sleep duration and efficiency were greater than those obtained through polysomnography. The reading level for this widely used measure is written at the 3rd-4th grade reading level and requires around 10 minutes.

Clinician Measures

Treatment Fidelity Checklist

These checklists include the therapist integrity goals, parent objectives and level of adherence for each SPT and SPE session. Therapists rate themselves on 5-7 session-specific goals on a scale of 0 to 2 as follows: (0 = Goal was not achieved; 1 = Goal was partially achieved; 2 = Goal was fully achieved). Therapists are asked to comment on items rated 0. Parent objectives and adherence are scored on a similar scale. The score for each session = sum of scores for all items in that session divided by the total possible score X 100. An example of a treatment fidelity checklist is in Intervention section. These treatment fidelity checklists have been modeled after four other previously NIH-funded projects.[31,97,148,191]

Safety/Adverse Event Review Form

Starting at the screen visit, the masked Independent Evaluator (IE) will ask about recent health complaints, use of medical services and concomitant medications. The Safety/Adverse Event Review Form also asks about the child's sleep, appetite and bowel habits. Screen data will be documented so that new adverse events can be elicited and recorded using the same Safety/Adverse Event Review Form. Reports of new adverse events or worsening of previously reported events will be rated mild (present, but not a problem), moderate (present, posing a problem or intervention required to prevent a problem) or severe (present, posing a problem and needed intervention). Hospitalization will be documented as a serious adverse event. A "yes" answer to any of these queries will prompt further questions to determine duration and severity. The onset, offset and severity of adverse events will be documented whether presumed to be related to the study treatment or not (see Human Subjects section).

Description of Interventions

Behavioral Parent Training for Sleep Disturbances (SPT)

SPT is an expanded version of the single sleep session that the PI (C. Johnson) developed for the RUPP Autism Network Parent Training (PT) program (U10MH66764] and the recently completed Research Units on Behavioral Intervention PT program [RUBI, R01MH1081148MH; Johnson, PI).[31,197,198] SPT was developed and evaluated for feasibility and initial test of efficacy (R34MH08288: Johnson, PI).[97] The five SPT sessions (each 60-90 minutes in duration) are individually delivered over 10-weeks (see Table 2). In addition to the five sessions, there are three home visits conducted via Express Care Online (HIPAA compliant video-chat). After Session A, session order may be adjusted to address child-specific problems. For example, if night wakings is the highest priority, Session C may be offered before Session B to introduce the use of extinction or scheduled wakings. Spreading the sessions over 10 weeks allows for scheduling flexibility and opportunities to present child-specific optional materials (outlined in Table 2). All parents/caregivers who are involved with the child's bedtime and sleep will be encouraged to participate. Hopefully, telehealth delivery will facilitate fuller

inclusion of caregivers. Each session employs direct instruction, modeling, and role-playing to promote parental skill acquisition. The SPT manual includes a therapist script and parent activity sheets for each session. Video vignettes have been developed for each session that model specific techniques and show a parent incorrectly applying the technique for different bedtime problems. For example, vignettes show a parent reacting to a child's tantrum at bedtime and a parent responding to a child calling out in the middle of the night. By showing ineffective parent management strategies, the video vignettes supplement direct instruction. In discussion, the parent is encouraged to identify the error in the vignette and to consider alternative responses. Thus, the video vignettes serve as a check on the parents' acquisition of concepts and techniques and permit the therapist to clarify uncertainties. Parents are given homework assignments to practice new skills learned in each session along with data collection assignments. The materials from one of the SPT session are provided in the Intervention section.

Rationale for SPT

Parent training based on the principles of applied behavior analysis is an empirically supported intervention for

Table 2. SPT Session Outline

Sessions	Topics Addressed
A. Importance of Sleep & Basic Behavioral Principles	• Introduce overall goals. • Introduce importance of sleep and the need to improve quality of sleep in children with ASD. • Introduce antecedent, behavior, and consequence model. • Introduce the concept of the functions of behavior. • Introduce general sleep hygiene guidelines. • View bedroom / sleeping environment
B. Addressing Prevention Techniques & Bedtime Routines	• Discuss preventive techniques .specific to children with ASD. • Develop daily schedule as well as bedtime schedule / routine. • Develop visual schedule that supports daily/bedtime routine. • Review how to develop social stories, when appropriate.
VSEE Evening Session	Parent coaching at bedtime
C. Addressing the Use of Extinction & Procedures for Bedtime Struggles, Night Wakings and Early Morning Wakings	• Introduce concept of extinction / planned ignoring to decrease behaviors. • Introduce use of different extinction techniques to specifically address sleep problems (bedtime struggles, night wakings, early morning wakings). • Introduce concept of reinforcers and teach contingent implementation of reinforcement. • Decide upon reinforcement, extinction, & scheduled awakening procedures.
VSEE Evening Session	Parent coaching at bedtime
D. Addressing Delayed Sleep Onset & Sleep Association Procedures	• Introduce the concept of stimulus control and its relationship to sleep behaviors. • Introduce faded bedtime routines as well as review bedtime routine. • Introduce teaching new sleep associations. • Develop specific procedures for teaching new sleep associations.
VSEE Evening Session	Parent coaching at bedtime
E. Booster & Maintenance Session	• Revise & "tweak" procedures / techniques based on review of sleep diary data and parent report of progress. • Discuss strategies for maintenance of behavior change. • Generate ideas of what to do if changes do not / have not maintained.
OPTIONAL MATERIALS *Address Noncompliance* *Address Nighttime Fears*	• Introduce concept of compliance / noncompliance • Review steps for compliance training • Review procedures for increasing compliance around bedtime and nighttime • Review why children may have fears at nighttime • Discuss with parent's their child's fears • Develop plan to reassure child, teach the child "brave skills" • Teach parents to implement systematic exposure for severe/specific fears

young children with ASD and disruptive behavior.[31] For sleep problems, parent training was also chosen for pragmatic reasons: a parent/caregiver is available at bedtime when sleep disturbances occur; and parents (and other family members) may be adversely affected by the child's sleep disturbance. The decision to have all participants complete the five-session SPT program, regardless of primary sleep complaint is based on the observation that children with ASD often have more than one sleep problem and sleep problems can change over time in this population.[97] Thus, SPT provides a comprehensive intervention that teaches parents the basic concepts and practical skills to address an array of sleep problems. One-on-one delivery of SPT permits flexibility for child-specific problems within the program.

Rationale and Modifications of SPT for Telehealth Delivery.

Telehealth delivery of SPT is expected to not only be more feasible in that it will allow families who live a distance from tertiary, specialized autism centers to participate, but is more optimal in that materials from the sessions may be delivered at a time more convenient for them; even soon before bedtime so content is fresh for parents. This will also allow us to complete more parent-child coaching in this manner of delivery. Overall, ecological validity of the intervention will be enhanced by delivering SPT via telehealth platform. Modifications to be made to allow for telehealth delivery are minimal. Session activity sheets the parents will need will be pushed out by REDCap ahead of time. Hard copies will also be mailed if families prefer. The video vignettes used in each session will be viewed via the split screen of Express Care Online. We can also provide the families with a DVD of the videos if they wish. Materials that might have been developed in session for the family to use at home (for example, a visual schedule) will be overnight mailed to the family as well as pushed out to them by REDCap link.

Sleep Parent Education (SPE)

SPE consists of five 60-90 minute sessions, delivered individually over 10 weeks. As with SPT, we expect one parent to attend all sessions, but another parent or caregiver is invited to attend SPE. As shown in Table 3, SPE provides useful information to families of young children with ASD and sleep problems. Session A is designed to develop rapport. The sleep hygiene session (Session B) has been modeled from the RUBI manual. The other

Table 3. Sleep Hygiene and Parent Education (SPE) Outline

Sessions	Goals & Topics Addressed
A. ASD Diagnosis	• Discuss diagnosis & family's adjustment • Prevalence of ASD in the population and etiology • Review service delivery models • Review sleep diary to be completed for next session
B. Sleep Hygiene	• Introduce types of sleep disturbances observed in ASD • Review CSI and Sleep Diary with parent(s) • Develop plan to address identified bedtime / sleep problems • Develop data collection to monitor progress
C. Understanding & Interpreting Clinical Evaluations	• What do IQ tests measure & understanding the scores • Speech, language and communication measures • Fine motor measures • Review selected behavioral ratings
D. Advocacy and Support Services	• Provide information about national & local support services • Parent to parent contact • Advocacy services and how to use them
E. Treatments & Treatment Planning	• Information on evidence-based / best practices • Information on other alternative treatments & use of supplements • Review of current services for child • Discuss progress and current concerns • Discuss other treatment options available for children with ASD

sessions include a systematic presentation on several relevant topics (see Table 3). An example of a SPE session is provided in the Intervention section. This control condition is intended to parallel what would be offered in typical care, but by telehealth, where a parent might be educated about ASD as well as attend an outpatient appointment at a sleep clinic.

Rationale for SPE as the control condition

SPE is a structured program intended to mimic competent *treatment as usual*. Thus, SPE is an accepted treatment and serves as an active comparator that controls for time and attention. We have conducted two previous randomized trials using parent education as the control condition. In both studies, attrition was low and satisfaction was high.[31,97]

Rationale and Modifications of SPE for Telehealth Delivery. Given our success with using SPE as an active comparator in previous studies, we are optimistic about using this control for the current study. As with SPT, minimal modifications will need to be made to deliver SPE individually via telehealth platform. All materials parents will need for SPE will be pushed out via REDCap, with the option of a hard copy mailed to them as well. In fact, telehealth delivery of SPE is more interactive than many internet-based programs that parents use to seek knowledge about ASD (e.g. Autism Speaks, Autism Navigator, Organization for Autism Research). Parents in SPE will receive the benefits of a therapist to respond to their specific questions and as aforementioned, parents in previous trials have been extremely satisfied with SPE.[31,97]

Quality Control

Assessments

Measures to be used for this study have all been used in prior studies by Dr. Johnson. At a start up meeting, the research team will review all measures. Dr. Johnson will review with independent evaluators (IEs) on the elicitation and documentation of the Parent Target Problems specifically around and to use all available information to rate the CGI-S and CGI-I, and to conduct the Safety/Adverse Event Review.

Therapist Selection, Training & Fidelity Monitoring

Doctoral or masters level practitioners with behavioral intervention experience in children with ASD will provide study treatments. Dr. Johnson, who has extensive therapist training experience, will train study therapist(s). Therapists will read through the treatment manual and observe sessions (or videos) by an experienced clinician delivering SPT and SPE. Similar to our other studies, therapists will be trained to 80% reliability for each session of both manuals with a non-study subject prior to treating randomized study subjects. The reliability will be confirmed by review of audio recordings by Dr. Johnson. After each SPT or SPE session, therapists will rate their own fidelity on a set of session-specific goals using a 0-2 scale (0=item not covered, 1=partially covered, 2=fully covered). All sessions in the randomized trial will be audio recorded and a 10% sample of randomly selected recordings will be scored to monitor therapist fidelity throughout the study. If therapist fidelity falls below criterion, a remedial plan will be implemented. Another element of treatment integrity is parental adherence (compliance and engagement). Therapists will rate parental adherence to SPT or SPE on a similar 0 to 2 scale. Parental adherence that falls below 70% in two successive sessions will be directly discussed with the parent. A session treatment fidelity form example may be found in the Intervention section along with session materials.

Data Management and Analyses

Data Management

Data will be collected directly via the web-based data entry site, developed through REDCap.[171] REDCap is a secure, web-based application for building and managing online surveys and databases. The REDCap software, training videos and basic end-user support are provided to all Cleveland Clinic investigators without charge. The system is managed by the Cleveland Clinic Center for Clinical Research and Learner Research Institute Research Computing Services. REDCap resides on servers within the Learner Research Institute. This centrally-located data center features redundant, high availability infrastructure components, including over 100TB of XIOTech SAN and SATA storage capacity, IBM Tivoli tape libraries for backup, HP servers, VMWare Virtual Infrastructure Clusters and a system-wide Liebert 130KVA Uninterrupted Power Supply. Data are backed up hourly at 3 separate, secure locations.

Data management analyst (TBN) under the direction of biostatistician (Sarah Worley) will develop the online data collection forms through REDCap. The data entry forms will be designed with as few open-ended text fields, and as many user-friendly drop-down answer boxes or check boxes as possible, with little opportunity for responses to be provided with implausible values. Clinic data will be entered by the study coordinators; the entry forms will be developed with built-in range checks and automatically-calculated fields to reduce the possibilities of data entry errors. Branching logic will be extensively used so questions/fields do not need to appear when they are illogical. The database will be pilot-tested after development, with feedback from the coordinator on ease of use. A separate randomization assignment data set will exist with a common identifier to allow for linkage with the study database for final analyses. This randomization data set will be maintained on a secure server and only accessible by the data management team. During enrollment, the data manager will regularly check for data inconsistencies, omissions, and errors, confirming with the coordinator when outliers and unusual values are observed. The data manager will randomly select 10% of data on a quarterly basis to be checked for data entry quality; discrepancies will trigger review of data collection and entry procedures as appropriate. The data management team will attend all study meetings to ensure constant communication about data issues that may arise throughout the study.

Sample Size and Power Calculation for Primary Hypotheses.

We base our power analysis on the primary aim/analysis comparing efficacy of SPT for sleep disturbance in children with ASD compared to SPE, with the CSI score as the primary outcome. Specifically, we aim to achieve 90% power to detect a meaningful difference in change in CSI scores between baseline and 10 weeks between the SPT and SPE groups ($\alpha = 0.05$). We assume we will have roughly 40 participants per group (80 total) after allowing for an attrition rate of about 10% in each group as has been average from our previous clinical trials. A 2-point difference in the CSI score (CSI description below) is clinically relevant. Based on our preliminary study (Figure 1), we observed a SD = 2.5 for the difference between baseline and 8-week CSI scores in the treatment group and a SD = 2.3 for the difference in the control group. The SD's for the 4-week difference were also equal to 2.3 in both groups; thus a conservative SD estimate of 2.5 for the difference between baseline and 10 weeks was used. For the parameters listed above and a total final sample size of 80, we will have 90% power to detect a difference in 10-week CSI change of 1.7 points or greater. Given the constant SD's observed over time, this power analysis is reasonable for 5-week comparisons as well. For hypothesis 2, specifically focusing on the CGI-I, we predict somewhere between 25%-40% positive response in the SPE group. With 45 per group (CGI-I drop-outs will be classified as negative responders by default), we will have 90% power (α=0.05) to detect a 32% or greater difference in positive response rate (57%-72%, respectively).

Statistical Analysis

Statistical analyses will be conducted by Sarah Worley in collaboration with the study team. We will begin with descriptive statistics for baseline data across treatment groups. Study coordinator and data manager will inspect data for errors, inconsistencies, and incomplete information across time points (as a follow-up to the regular data management procedures that will occur throughout the study, described above). This will include examination of frequency tables and scatter plots. Data anomalies and outliers will be examined and corrected if necessary. These preliminary analyses will include descriptive statistics in each treatment group for all outcome variables, plots of longitudinal data over time, and examination of distributions within groups at important nodal points (e.g., Baseline, Week 5, 10 and 16). For the **primary analysis**, we will use a linear mixed model, which will make use of the repeated measurement of the CSI. Specifically, we will model change in CSI relative to baseline at weeks 5 and 10 (and week 16), with primary fixed effects of baseline CSI, treatment (SPT or SPE), time, and the interaction between time and treatment. No systematic trend with time will be initially assumed to allow for potential nonlinear trends; if linear changes are observed (and confirmed via statistical testing), we will model time as a continuous variable. With at most three repeated measurements, model selection of the covariance structure is minimized; we will model directly the variance of the outcome at each time point as well as the correlation between the three visits (i.e., unstructured covariance). We will examine whether the covariance needs to be modeled separately between the two treatment groups, as well as whether

we can use a more parsimonious covariance model to maximize statistical power. Common model selection criteria will be used for this examination.[199] Appropriate assumptions and model conditions will be verified prior to analysis. Tabled data will be presented as differences in means across time with 95% confidence intervals. The Kenward-Roger approximation for the denominator degrees of freedom will be utilized to ensure valid inference of the fixed effects.[200] A similar approach will be used for the key continuous secondary outcome (Total Sleep Time on actigraph) and other secondary measures such as the ABC- Irritability subscale, PSI scales, Parental Competence measure, etc. The **key secondary analysis** will use the chi-square test to compare the rate of positive response on the CGI-I in SPT versus SPE. Chi-square tests will also be used to compare the rates of adverse events across treatment groups.

Efficacy analyses will follow the *intention-to-treat* convention (including all randomized subjects). For modeling and hypothesis testing, the proposed likelihood-based approach regards missing data as missing at random (MAR; i.e., missing data are independent of unobserved data). Although there is no proven method for verifying the MAR assumption, the likelihood-based solutions are robust to violations of ignorable missing data (i.e., situations where the MAR assumption is not met).[201] Prior to analyses for efficacy, we will examine the degree of randomness in missing data by comparing the frequency, reasons, pattern and time to dropout and missing values across treatment groups. If substantial differences in *missingness* occur across SPT and SPE that cannot be adequately explained by observed variables, secondary sensitivity analyses employing the methods described by Carpenter and Kenward[202] will be employed. These techniques will be considered cautiously in our analyses as they require certain assumptions that cannot be evaluated from the data under analysis. All analyses will be conducted using SAS v9.4 for Windows (Cary, NC, USA).

Given the planned sample size, we will not have sufficient statistical power to detect effect modifiers (i.e., compare the efficacy of the intervention among subgroups). However, we do plan to examine and compare the efficacy of the intervention between subgroups via statistical interactions in the above models. Variables of interest include age, IQ, and gender. These estimates, if we observe possible differential effects, will serve as the basis for future, larger studies that target the comprehensive study by subgroups.

The above general analysis plan holds for the majority of our aims/hypotheses. We discuss specifics analysis considerations below for each aim/hypothesis as appropriate.

Primary Aim

To evaluate the efficacy of telehealth delivery of SPT for sleep disturbance in children with ASD compared to telehealth delivery of SPE.

Hypothesis 1: After 10 weeks of treatment, children whose parents receive SPT will show greater reduction on the CSI from the MSPSQ compared to those whose parents receive SPE. *Our modeling approach above describes how we will test this hypothesis, with change in CSI relative to baseline as our outcome to be modeled over the span of the study via linear mixed models (5 and 10 weeks).*

Hypothesis 2: After 10 weeks of treatment, children in the SPT group will show significantly higher rates of positive response than children in the SPE group on the Improvement scale of the Clinical Global Impression (CGI-I) rated by an independent evaluator masked to group assignment. *The proportion of positive response (Much Improved or Very Much Improved) in SPT vs SPE will be tested using a Chi Square test.*

Hypothesis 3*:* After 10 weeks of treatment, children whose parents receive SPT will show significantly lower rates of disruptive behaviors on the parent-rated ABC-Irritability subscale compared to children whose parents receive SPE. *To test this hypothesis, we will use the same linear mixed model approach described for the CSI.* The other ABC subscales will be examined in exploratory analyses.

Hypothesis 4: As noted above, all subjects will be asked to return at Week 16 to evaluate the post-treatment effects of SPT and SPE. Parents will rate the CSI. The same treatment blinded IE will rate the CGI-I at post-treatment follow up. *We will essentially add the 16-week CSI measure to the modeling framework described above to further characterize CSI trends over a longer period of time, and to compare these trends between the two groups. This modeling approach (in particular modeling the time point directly (i.e., not assuming a linear trend from baseline) will allow us to directly test for differences at 16 weeks. We will also compare the rate of*

*positive response on the CGI-I in the SPT versus SPE. Subjects who drop out before or after Week 10 will be classified as negative responders by default. *

Secondary Aim

To evaluate the impact of SPT on parental quality of life (parental stress, sense of competence, mental health and sleep) compared to SPE.

Hypothesis 1 and 2: After 10 Weeks of treatment, parents in SPT will report lower levels of stress and higher levels of competency and overall health as measured by the PSI (stress), PSOC (competence), PHQ (mental health) and better PSQI (sleep) than parents in SPE. *To test these hypotheses, we will use the same linear mixed model approach described for the CSI. Exploratory analyses will test whether parental quality of life shows greater change from baseline to week 16 on the PSI, PSOC, PSQ, and PSQI compared to SPE.*

Timetable of Projected Activities

A total of 90 children will be recruited. In the second half of Year 01, each site will screen 17-18 subjects with the goal of randomizing 15 subjects. In Years 2 and 3, we aim intend to randomize 30 subjects per year. In the first half of Year 04, we will screen 17-18 subjects to meet goal of randomizing the final 15 participants (see Table 4).

Table 4. Timetable	Month 0-6	Month 6-12	Year 02	Year 03	Year 04
IRB approval finalized	X				
Set Up Entry Programs	X				
Train Therapists	X				
Recruitment & Enrollment		X	X	X	X
Conduct Interventions		X	X	X	X
Follow-Up Assessments		X	X	X	X
Data Analysis					X
Manuscript Preparation					X
Dissemination					X

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