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Short Title	PAP for children with DS and OSAS
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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ABAS	Adaptive Behavior Assessment
ADHD	Attention deficit hyperactivity disorder
AHI	Apnea hypopnea index
BRIEF	Behavior Rating Inventory of Executive Function
BMI	Body mass index
BP	Blood pressure
CBCL	Child Behavior Checklist
CHOP	Children's Hospital of Philadelphia
CCHMC	Cincinnati Children's Hospital Medical Center
CCC	Clinical Coordinating Center
CRF	Case report form
DCC	Data Coordinating Center
DMS	Data Management System
DS	Down syndrome
DSMB	Data Safety and Monitoring Board
EDC	Electronic data capture
EMR	Electronic medical record
GNG	Go-No-Go
HCU	Health care utilization
IRB	Institutional Review Board
MOP	Manual of procedures
NHLBI	National Heart Lung Blood Institute
OAI	Obstructive apnea index
OSAS	Obstructive sleep apnea syndrome
PedsQL	Pediatric Quality of Life Inventory
PAP	Positive airway pressure
PSQ	Pediatric Sleep Questionnaire
PSG	Polysomnogram
RCT	Randomized controlled trial
SDB	Sleep-disordered breathing
SES	Socioeconomic status

ABSTRACT

Context: (Background)

- OSAS is very common in children with DS
- OSAS in children with DS does not resolve after adenotonsillectomy
- Many children with DS and OSAS require treatment with PAP

Objectives:

- Determine the efficacy of a 6-month intensive behavioral intervention (INT) vs. standard care (SC) in promoting PAP adherence in children with DS and OSAS who are naïve to PAP or have not used PAP for the past 3 years prior to enrollment
- Evaluate the effect of PAP adherence on quality of life, neurobehavioral functioning, and healthcare utilization in children with DS and OSAS
- Evaluate the effect of PAP adherence in children with DS and OSAS on patient-centered outcomes and family-relevant outcomes.

Study Design:

- Randomized Controlled Trial

Setting/Participants:

- The study will be performed at Children's Hospital of Philadelphia (CHOP), Cincinnati Children's Hospital Medical Center (CCHMC) and University of Miami outpatient setting
    - 3 Sites
- 100 participants with DS and OSAS will be recruited after clinical referral for PAP
- Clinical referral for PAP initiation to treat OSAS
- Age between 6-18 years
- Naïve to PAP treatment or have not used PAP for the past 3 years prior to enrollment

Study Interventions and Measures:

Six-month intensive family-based behavioral intervention (INT) vs Standard care (SC)

Main study outcome measures to be measured at 6 and 12 months after PAP initiation

Primary Outcome Measure: Percentage of Nights Adherent to PAP Therapy from Initiation to 6 Months. PAP adherence will be assessed as the percentage of nights in which the participant is adherent to PAP therapy from initiation (T0) through 6 months (T6). This is calculated as the number of nights meeting adherence criteria divided by the total number of nights during the participants study participation period, multiplied by 100. [Time Frame: 6 months]

Secondary Outcome Measures:

- Number of Minutes of PAP Used on Nights Used: PAP adherence will be measured as the number of minutes of PAP use per night among nights with any recorded PAP use, calculated per participant from PAP initiation through the end of the 6-month intervention period. [Time Frame: 6 months]

- Change in PedsQL Total Score (Quality of Life) : Quality of life will be measured using the Pediatric Quality of Life Inventory (PedsQL) total score. The PedsQL is a 5-point scale ranging from 0 to 4 (0 = Never, 4 = Always), with higher scores indicating better quality of life. [Time Frame: Baseline, 6 months, and 12 months]

- Change in Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) Parent Report Score . Executive functioning will be assessed using the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2), a parent-reported questionnaire that evaluates behaviors associated with executive functioning. Scores are reported as standardized T-scores, with higher scores indicating greater executive dysfunction. [Time Frame: Baseline, 6 months, and 12 months]

Percentage of Nights Adherent to PAP Therapy from Initiation to 12 Months: PAP adherence will be assessed as the percentage of nights in which the participant is adherent to PAP therapy from initiation (T0) through 12 months (T12). This is calculated as the number of nights meeting adherence criteria divided by the total number of days during the participants study participation period, multiplied by 100. [Time Frame: 12 months]

PROTOCOL SYNOPSIS

Study Title	Positive Airway Pressure For The Treatment Of The Obstructive Sleep Apnea Syndrome In Children With Down Syndrome
Funder	NIH/NHLBI
Clinical Phase	Phase IV
Study Rationale	5,400 children with DS born in the USA annually. Hallmarks of the syndrome include intellectual disability, hypotonia and craniofacial anomalies, and congenital cardiac defects occur in 50% of individuals. Common comorbidities include hypothyroidism, obesity, and the obstructive sleep apnea syndrome (OSAS). Untreated OSAS is associated with significant morbidity such as growth failure, systemic, and pulmonary hypertension, endothelial dysfunction, and cognitive and behavioral deficits. Median life expectancy in individuals with DS has increased from 25 years in 1983 to 58 years in the present day. While this represents a significant advance in health, individuals with DS still have early mortality compared to the general population. It is therefore incumbent upon health care practitioners to diagnose and treat comorbidities, such as OSAS, in order to optimize health and cognitive/behavioral function, increase survival, and maximize health-related quality of life. Individuals with DS are predisposed to OSAS due to craniofacial features (midface hypoplasia, glossoptosis), hypotonia, comorbid obesity, and hypothyroidism. Studies have shown a prevalence of OSAS in children with DS between 45 and 55%. These rates are markedly higher than that of typically developing children in whom the prevalence of OSAS is about 2%. Adenotonsillectomy (AT) is considered first-line treatment for childhood OSAS. However, available data indicate that polysomnography (PSG) improves in only a portion of children with DS after AT. Many children with DS are referred for positive airway pressure (PAP) therapy initiation due to persistent OSAS after AT, and PAP appears to be an important feature of the experience of living with DS. PAP has been shown to be highly effective at resolving polysomnographic manifestations of OSAS in children and adolescents, including those with DS and other disabilities. Importantly, studies indicate that PAP also reduces symptoms of OSAS and improves school performance, behavior, mood, daytime sleepiness and quality of life in typically developing children and adolescents. However, PAP as a treatment for OSAS has not been well-studied in children with DS. Furthermore, patient/family reported outcomes are an important knowledge gap long overdue in this population. The overall aim of this proposal is to conduct a randomized controlled trial of standard clinical care (SC) compared to a 6-month intensive family-informed intervention (INT) to promote PAP adherence in children with DS and OSAS.
Study Objective(s)	**Primary** 1) Determine the efficacy of a 6-month intensive behavioral intervention (INT) vs. standard care (SC) in promoting PAP adherence at 6 months after PAP initiation in children with DS and

	OSAS naïve to PAP or have not used PAP for the past 3 years prior to enrollment **Secondary** 2) Determine the efficacy of a 6-month intensive behavioral intervention (INT) vs. standard care (SC) in promoting PAP adherence at 12 months after PAP initiation (6-month after the end of the intervention) in children with DS and OSAS naïve to PAP or have not used PAP for the past 3 years prior to enrollment 3) Evaluate the effect of PAP adherence on quality of life, neurobehavioral functioning, in children with DS and OSAS. **4)** Evaluate the effect of PAP adherence in children with DS and OSAS on patient-centered outcomes and family-relevant outcomes **Exploratory** 5) Use mixed methods during the randomized controlled trial to identify family perceptions, such as empowerment and self-efficacy, regarding PAP use in youth with OSAS and DS. 6) Evaluate the effect of PAP adherence on healthcare utilization.
Test Article(s) *(If Applicable)*	The intervention program is a multicomponent family-based intervention consisting of cognitive and behavioral strategies, including operant learning and contingency management, as well as motivational enhancement and engagement strategies, with an emphasis on caregiver involvement.
Study Design	Overview of design. Explain the basic design such as parallel group randomized controlled trial, open-label single arm PK study, diagnostic test evaluation, etc.
Subject Population **key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1. Subjects age 6-17.9 years 2. Diagnosis of DS 3. Clinical referral for PAP initiation to treat OSAS 4. Naïve to PAP or have not used PAP for the past 3 years prior to enrollment **Exclusion Criteria** 1. Child with major illness, such as leukemia or severe cyanotic congenital heart disease listed for cardiac transplant 2. Family planning to move out of the area within the year 3. Child in foster care 4. Caregivers who do not speak English well enough to complete behavioral and performance measures.
Number Of Subjects	Total Number of Subjects: 86, Total Number at CHOP: 43, Total Number of Sites: 3
Study Duration	Each subject's participation will last 12 months. The entire study is expected to last 3 years.

Study Phases **Screening** **Study Treatment** **Follow-Up**	1) Screening: screening for eligibility and obtaining consent, 2) Intervention: study intervention for 6 months, including intervention visits at months 1, 3, and 6, 3) Follow Up Assessments at Months 6 and Month 12 after the 1st visit.
Efficacy Evaluations	Objective adherence data transmitted from the PAP device.
Pharmacokinetic Evaluations	NA
Safety Evaluations	Clinically significant worsening of neurobehavioral outcomes.
Statistical And Analytic Plan	Primary Outcome: PAP adherence from PAP initiation (T0) to the end of the 6-month intervention (T6) between the 2 arms. PAP adherence will be expressed as percentage of nights used, and minutes of use on nights used during this 6-month period. This will be first tested with a two-sample t-test if the data are normally distributed, and the Wilcoxon rank sum test if not. PAP predictive factors for adherence at 6 months will be evaluated by multiple linear regressions, including possible confounding factors, some of which may be identified during the R61 phase of this proposal. The distribution of the outcome variable will be assessed visually and statistically, and transformation can be applied to meet the normality assumption required by linear regression. Stepwise model selection algorithm may be applied to help determine the final model. Secondary Outcomes: -PAP adherence from the end of the 6-month intervention (T6) to 12 months after initiation (T6 to T12) between the 2 arms. This will allow us to evaluate the effect of the intervention 6 months after the end of the intervention. PAP adherence will be defined the same way as in T0-T6 period. Similarly, this will be tested with a t-test or Wilcoxon rank sum test as appropriate, and potential PAP factors associated with adherence from T6-T12 will be evaluated by multiple linear regressions. We are also interested in assessing whether the improved adherence is maintained over 12 months within each arm using a paired t-test or its nonparametric equivalent as appropriate to compare the adherence in T0-T6 to that of T6-T12 separately for each arm. We will also perform a linear mixed-effects model for each arm on the adherence in the two time periods, adjusted for covariates of the interest. In this model, the time period will be the independent variable, e.g., 0 for T0-T6 and 1 for T6-T12, and we test whether the slope of time differs from 0. This model accounts for within-subject correlation due to repeated measures by including a subject-specific random effect. In addition, we would like to evaluate whether INT group maintains a better adherence as compared to SC group. To test this hypothesis, we will similarly perform a linear mixed-effects regression but for all subjects with an interaction term of time x group, adjusted for baseline adherence (i.e., adherence in T6-T12) and other covariates of interest. Testing this interaction term will tell us whether one arm maintains a better adherence than the other arm over the 12 months period.

	-Quality of life (QOL) and neurobehavioral changes between the 2 arms will be tested with a t-test if the data are normally distributed, and the Mann-Whitney-Wilcoxon test if not. One-way ANOVA will be utilized to test differences in QOL and neurobehavioral outcomes within groups at 0, 6, and 12 months if data are normally distributed. If not, one-way ANOVA on ranks will be utilized. Longitudinal models using generalized estimating equations (GEE) will be fitted to explore effects of randomization on QOL and neurobehavioral changes. An indicator variable for randomization, time, and a time by randomization group interaction term will be included in the models. If the interaction term differs significantly from zero, this will indicate that the change over time in the outcome of interest differs significantly between the two arms. In the longitudinal model using GEE to assess the intervention effect on the QOL and neurobehavioral outcomes over time, we will include the PAP adherence as well as an interaction of group by adherence, where the PAP adherence is measured as percentage of nights used and minutes of use on nights used. By testing these interaction terms, we will be able to determine whether the intervention effect on the outcomes is modified by the adherence level. We will assess the sensitivity of results to the choice of working correlation structure that models association in the GEE analyses. We will also implement quasi-least squares (QLS), an approach based on GEE that allows for implementation of the Markov correlation structure. The Markov structure is plausible if participants have unequal temporal spacing of their measurements. In addition, we will consider the application of mixed effects models if the assumptions of these models are met. The baseline obstructive apnea hypopnea index will be included in the model, and potential confounding variables such as age, gender, race, socio-economic status and BMI will also be included in the models. Mixed Methods Outcome: Coded data will be summarized, examined for patterns and used to identify factors associated with adherence and non-adherence as well as implementation. Data between the 2 randomization arms will be compared.
DATA AND SAFETY MONITORING PLAN	NIH-appointed DSMB and Independent Safety Monitor (Dr. Toshihiro Imamura)

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Treatment/ Intervention**							**Follow-up**
Visit Number for		**PAP initiation baseline visit**	**1 Month Visit**	**Phone Calls from Psych INT**	**Phone Calls-Family Initiated SC**	**Phone Calls From Research Coordinator**	**3 Month Visit**	**6 Month Visit**	**12 Month Visit**
Study Days		On same date or within two weeks of neurobehavioral assessments		Weeks 1, 2, 6, 8, 10, 14, 20	As Need, initiated by family	Months 2, 4, 5, 7, 8, 9, 10, 11			
Informed Consent	X								
Review Inclusion/Exclusion Criteria	X								
Demographics/Medical History	X								
Physical Examination	X		X				X		
Height and Weight	X								
Prior/Concomitant Medications	X								
Questionnaires	X							X	X
Neurobehavioral Assessments	X							X	X
Randomization	X								
Initiation of PAP, including being fit for		X							

mask and provided equipment									
Adverse Event Assessment			X	X	X	X	X	X	X
Adherence Downloads			X	X			X	X	X
Healthcare Utilization			X	X	X	X	X	X	X
Parent and subject Qualitative Interviews in Subset of 20 Participants at CHOP, Cincinnati and University of Miami								X	X

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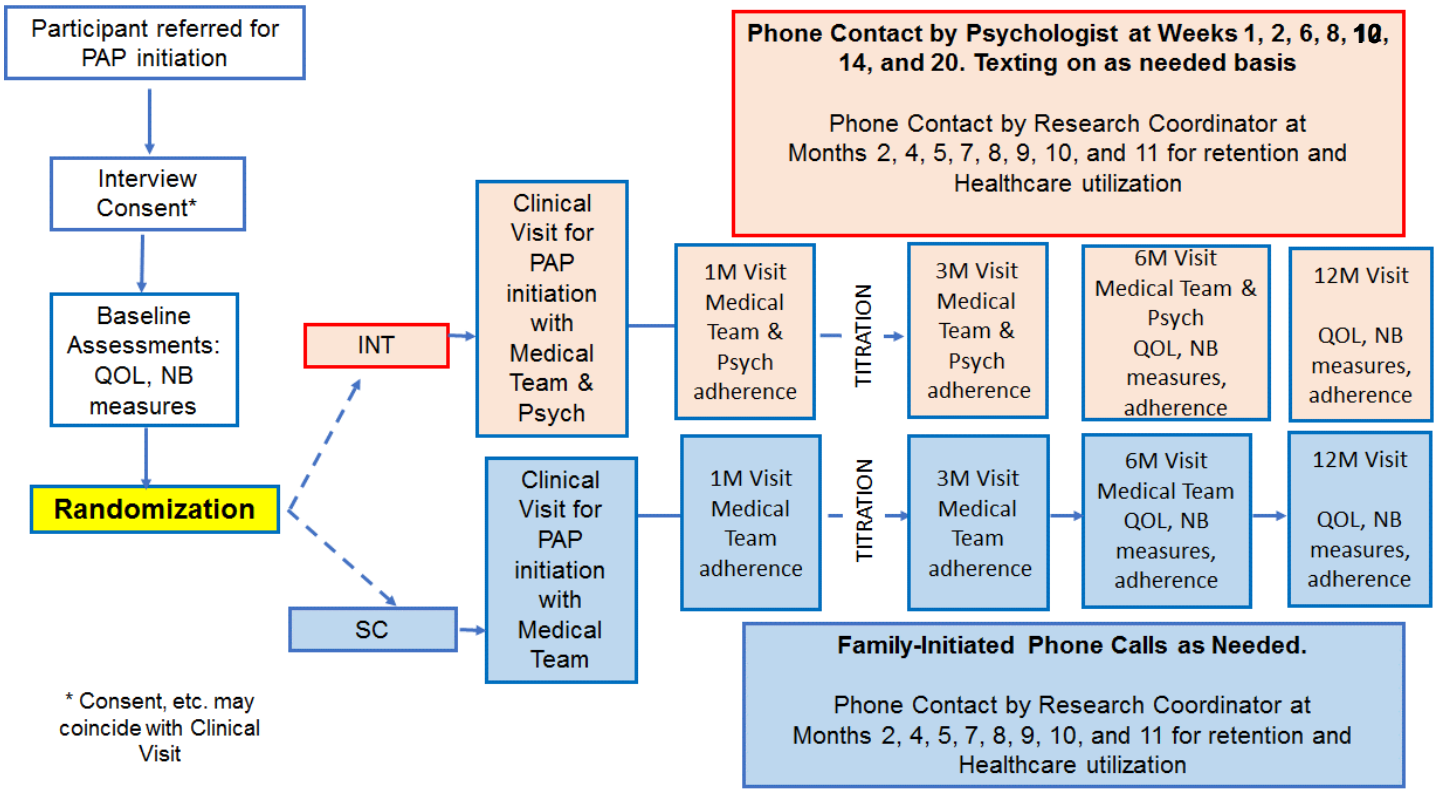
FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

5,400 children with DS born in the USA annually[1-4]. Hallmarks of the syndrome include intellectual disability, hypertonia and craniofacial anomalies, and congenital cardiac defects occur in 50% of individuals[5]. Common comorbidities include hypothyroidism, obesity, and the obstructive sleep apnea syndrome (OSAS). Untreated OSAS is associated with significant morbidity such as growth failure[6], systemic[7,8], and pulmonary hypertension[9,10], endothelial dysfunction[11,12], and cognitive and behavioral deficits[13,14]. Median life expectancy in individuals with DS has increased from 25 years in 1983 to 58 years in the present day[15,16]. While this represents a significant advance in health, individuals with DS still have early mortality compared to the general population. It is therefore incumbent upon health care practitioners to diagnose and treat comorbidities, such as OSAS, in order to optimize health and cognitive/behavioral function, increase survival, and maximize health-related quality of life. Individuals with DS are predisposed to OSAS due to craniofacial features (midface hypoplasia, glossoptosis), hypotonia, comorbid obesity, and hypothyroidism. Studies have shown a prevalence of OSAS in children with DS between 45 and 55%[17,18]. These rates are markedly higher than that of typically developing children in whom the prevalence of OSAS is about 2%[19].

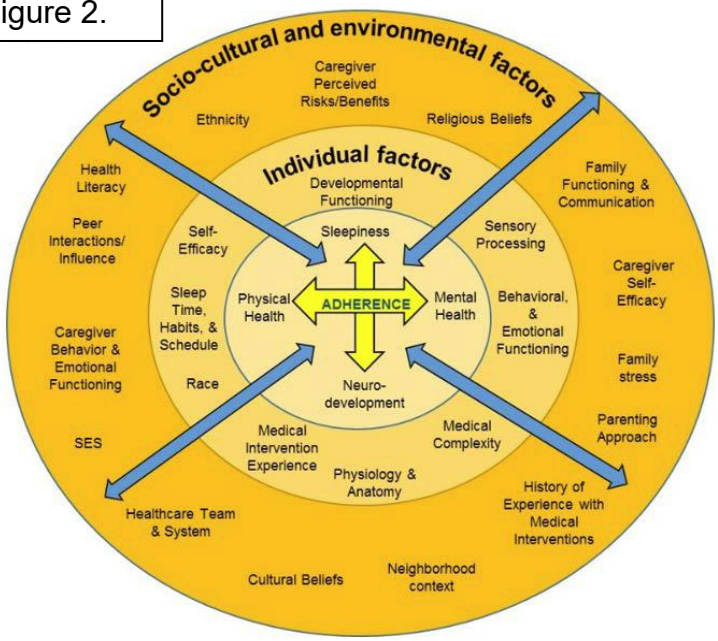
Adenotonsillectomy (AT) is considered first-line treatment for childhood OSAS[20]. However, available data indicate that polysomnography (PSG) improves in only a portion of children with DS after AT[21]. Many children with DS are referred for positive airway pressure (PAP) therapy initiation due to persistent OSAS after AT[22], and PAP appears to be an important feature of the experience of living with DS. PAP has been shown to be highly effective at resolving polysomnographic manifestations of OSAS in children and adolescents, including those with DS and other disabilities[20,23]. Importantly, studies indicate that PAP also reduces symptoms of OSAS and improves school performance, behavior, mood, daytime sleepiness and quality of life in typically developing children and adolescents[13,20]. However, PAP as a treatment for OSAS has not been well-studied in children with DS. Furthermore, patient/family reported outcomes are an important knowledge gap long overdue in this population. The overall aim of this proposal is to conduct a randomized controlled trial of standard clinical care (SC) compared to a 6-month intensive family-informed intervention (INT) to promote PAP adherence in children with DS and OSAS.

1.2 Name and Description of Investigational Product or Intervention

Standard Care (SC): Participants in SC will receive usual clinical care that is what is typically provided at medical teams in pediatric sleep centers. At the initiation visit, participants assigned to SC will meet with the physician and nurse to discuss the diagnosis and treatment with PAP. They will be provided hand-outs on recommended amounts of sleep, healthy sleep habits, positive parenting strategies, and desensitization. They will also receive the phone number for the study Sleep Clinic nurses to call with any questions. At the three 30-minute follow-up visits, the PAP device will be downloaded and feedback about use of PAP by the participant will be provided to the family by the medical team; the equipment will be checked and a physician or nurse will review any medical concerns. The family will be provided the phone number for the medical team should they have questions, need support, or want to review the modem data and change the behavioral plan.

Family-informed intervention (INT): INT will have multiple face-to-face visits and phone calls and visits with the PAP psychologist and medical team. Follow up visits will last about 30-45 minutes. At each visit, PAP adherence will be downloaded from the modem and reviewed, problem solving and a further behavioral plan will be discussed, questions/concerns will be addressed, equipment will be checked and the physician investigator will systematically review medical concerns and side-effects. The psychologist will review progress based on downloads; discuss strategies to optimize adherence, tailored to the family and youth's needs; and discuss non-food based contingency rewards based on adherence to goals of each family. The socioecological model is the theoretical foundation for which the intervention is based (Figure2) and further specific details regarding the intervention are found in the grant application on pages 159-161. Phone calls will be made for continued engagement, review of downloads and retention, as well as to provide external accountability, problem solving, and reinforcement.

Figure 2.



Intervention Rationale: Children with DS often have difficulty with changes in routine[24]. As such, compared to other children, interventions for children with DS must place greater emphasis on repetition and consistency. Children with DS can also have difficulty with transitions[24]. Consequently, our intervention emphasizes use of visual supports, structured routine, consistent practice of skills, and transition cues. Children with DS are commonly described as stubborn, impulsive, and frequently noncompliant; refusal behavior may contribute to nonadherence[24]. To accommodate, we will place emphasis on addressing these behaviors in the bedtime routine, including the use of social stories, visual schedules, and gradual incorporation of PAP into the bedtime routine. Children with DS tend to have a relative strength in visuo-spatial processing[25]. Our manualized intervention will capitalize on this by emphasizing daily practice and progressive desensitization with positive reinforcement and visual cues. The INT-PAP program is a multicomponent family-based intervention consisting of cognitive and behavioral strategies, including operant learning and contingency management, as well as motivational enhancement and engagement strategies, with an emphasis on caregiver involvement based on the adherence literature[26] and clinical experience; these are approaches that have been shown to promote health behavior change and adherence[26,27]. The overall goals are to increase the perceived importance of PAP treatment, improve confidence in the ability for the caregiver to implement PAP at home, and support the family in integrating PAP into the family's routine. We will use healthcare adherence promotors to facilitate adherence,

including outreach promotors (e.g., phone calls, text messaging) and concrete promotors (e.g., providing travel expenses).

1.3 Relevant Literature and Data

PAP adherence in children with DS: There is a dearth of literature regarding PAP adherence in children, and even less in children with DS[28,29]. Generally, PAP is inherently difficult for individuals to use regularly. In addition to the burden of putting the equipment on each night and possible (initial) discomfort of wearing a mask with pressurized air administered during sleep, and common side-effects including nasal symptoms (e.g., nasal dryness, rhinorrhea, congestion and epistaxis), eye irritation, skin pressure sores or dermatitis, and aerophagia. Some patients suffer from feeling closed-in by the mask (e.g., claustrophia). Not surprisingly, PAP efficacy is limited by poor adherence[30]. Importantly, the few studies, all retrospective, including children with DS under the larger umbrella of children with developmental disabilities (DD), have shown better adherence in children with DD compared to typically developing children[22,31]. Hawkins et al reported that DD was a positive predictor factor for PAP adherence (OR = 2 .55, 95%CI = 1.27–5.13; p = 0.007), and our group has showed that at 3 months after PAP initiation, adherence was 86.7% [33.9-97.9%] of nights in children with developmental disabilities and 62.9% [30.8-87.8%] in typically developing children (p=0.01)[31].

PAP adherence in youth with DS and OSAS: A retrospective study was performed of clinical records at CHOP of 61 youth with DS-OSAS (8.9±5.5 years; 53% females; 56% White) initiated on PAP over a 3-year period. Children had clinical follow up for at least 2 years following initiation by the same interdisciplinary team described in the current proposal. Adherence to PAP at 0-6, 6-12, 12-18, and 18-24 month intervals after initiation was analyzed. Data are presented as mean SD, median [IQR] or percentage. PAP adherence expressed as percentage of nights was 42.1[17.1-78.6] at 0-6 months, 63.6[14.3-92.4] at 6-12 months, 64.0[7.7-96.4] at 12-18 months, and 66[29.0-97.4] at 18-24 months. PAP adherence expressed as minutes used on nights used was 126[31.8-358.5] at 0-6 months, 237[77.0-438.5] at 6-12 months, 268.5[83.8-423.2] at 12-18 months, and 219.0[62.0-474.5] at 18-24 moths. Of those with adherence data at each time interval (N=21), the median minutes used was 184 mins at 0-6 months, 290 mins at 6-12 months, 321 mins at 12-18 months, and 219 mins at 18-24 months (p=0.008). These data show that PAP is feasible in children with DS and that adherence improved over time.

Health-related Quality of Life in youth with DS: In a study led by Dr. Melissa Xanthopoulos, co-investigator of this project, caregiver-rated QOL (PedsQL) was obtained from 150 caregivers of youth with DS aged 14.6 +3.3 years and 59 caregivers of youth without DS of comparable age, sex, race, ethnicity and BMI-Z score. In this cohort, mean caregiver-reported Total QOL was 68.1+ 13.8 for DS *vs* 82.1 + 15.3 in typically developing youth (note that a higher score reflects a better QOL)[32]. Youth with DS may have a lower QOL than their peers for a variety of reasons, but OSAS is likely a contributing factor. In typically developing youth, it has been shown that treatment of OSAS has a large impact on QOL[33]. In another study of our group, a heterogeneous group of 58 children and adolescents requiring CPAP therapy for OSAS, which included 6 youth with DS, we showed a significant improvement in both caregiver- (p=0.005) and youth-rated PedsQL (p<0.001) and OSA-18 (p< 0.001) scores after 3 months of CPAP therapy[13]. In the small subsample of youth with DS, parental-rated PedsQL score increased from 62.9 + 15.2 at baseline to 71.9 + 8.3 on CPAP (p = 0.08). The OSA-18 improved significantly, declining from 52.8 + 6.5 at baseline to 33.7 + 6.7 on CPAP, p = 0.001 (note that a lower score reflects a better

QOL on this measure). Thus, children with OSAS have decreased QOL that improves with treatment, and even in youth with DS, CPAP results in improved QOL despite the burden of care imposed by the treatment. In the proposed study, we will evaluate the difference in QOL between DS-OSAS and DS-SC, and correlate changes in QOL with PAP adherence regardless of the randomization arm.

General techniques. Polysomnography: Overnight polysomnography will be performed in a dedicated pediatric sleep laboratory as previously described[34]. The following parameters will be determined using standard pediatric techniques and scoring:[35] sleep architecture, respiratory events, arterial oxygen saturation (SpO_2), end-tidal carbon dioxide tension (ETCO2), and optimal positive airway pressure. Studies will be interpreted by the Data Coordinating Center.

Neurobehavioral Testing (NBT): Participants will undergo an NBT battery consisting of two tests performed by the participants at baseline, 6, and 12 months; performed at a standardized time in the morning after a usual night's sleep at home and administered by a blinded trained research coordinator. The 6-month interval was selected based on previous research showing improvement in some NBT measures 6 months after surgery[36] and 3 months after continuous positive airway pressure therapy in typically developing children[37]. Testing will take approximately 30 minutes for the child (Pegboard followed by Go-No-Go). The caregiver will be asked to complete questionnaires either in person or virtually and will take about 90 minutes. The battery is designed to evaluate QOL and constructs that have been associated with OSAS and its treatment (i.e., memory, attention, executive functioning, and daytime sleepiness). Caregivers will complete measures to supplement those administered directly to the subjects and must be completed within 2 weeks of child performance measures. The testing battery includes standardized caregiver ratings of behavior, quality of life, daily functioning, as well as performance tests of fine motor skills and attention (9-Hole Pegboard and Go-No-Go tests)[38]. Children with DS tend to do best on tasks that are more concrete and can be easily visualized and both tasks meet these requirements. As we recognize that many young children with DS will find even these tasks challenging, we will modify procedures for introducing these tasks to optimize engagement. Examples will include opportunities to pick up and place peg prior to beginning the pegboard task, and practice in pressing the button to examine signals prior to beginning the Go-No-Go task. The early childhood version of the Go-No-Go task will be used to account for the wide developmental variability in children with DS. These modifications will help ensure maximal engagement of the children in the testing and allow us to obtain additional information on the performance of children who are unable to complete the tasks. Trained test administrators will complete a structured appraisal form for each testing session that rates the ability of children to complete each task, including information on why a children was unable to complete the task (e.g., ability to understand task, visual/motor delays, etc.) The primary outcome of NBT will be QOL measured by the Pediatric Quality of Life Inventory (PedsQL).

Objective Performance Tests:

- *Vigilance:* The Go-No-Go Continuous Performance Task[38] will provide an objective measure of sustained attention (vigilance), which is considered a fundamental factor influencing executive functioning and behavior. The computerized Go-No-Go will allow us to assess whether observed changes in behavior are accompanied by objectively measured changes in attentional abilities. The test is easy to administer and appropriate for children as young as 3 years. In this task, children are presented with pictures of colored fish and sharks and asked to respond to only the fish using a button box.

- *Fine motor coordination:* The NIH Toolbox 9-Hole Pegboard Dexterity Test is a test of fine motor coordination that has been shown to be abnormal in adults[39,40] and children[36] with OSAS.

Caregiver rating scales and their constructs. The following scales will be used:

Quality of life and symptoms:

- Generic Quality of life: The Pediatric Quality of Life Inventory (PedsQL) is a well-validated, generic measure of global quality of life that will be obtained by caregiver proxy and has been used in children with DS.[32]
- Disease-specific quality of life: The OSAS-18 is a validated caregiver questionnaire comprising assessments of SDB symptoms and disease-specific quality of life that has been shown to improve after OSA treatment.[41]
- OSA symptoms: The caregiver-completed Pediatric Sleep Questionnaire (PSQ) is the most validated questionnaire assessing OSA symptoms.[42]
- Pediatric sleep disorders: The Children's Sleep Habits Questions (CSHQ) is a well-validated screener across multiple domains of common sleep disorders in children.[43]

Family functioning measures:

- Family Assessment Device, a survey of 7 domains of family functioning, including aspects such as problem solving and communications.[44]
- Parenting Style Questionnaire, a survey of the type of parenting style (authoritative, authoritarian or permissive).
- Parenting Stress Index Short Form, an assessment of parents' perception of stress in the parent-child system.
- Rapid Estimate of Adult Literacy in Medicine - Short Form, a 7-item word recognition test that provides a rapid assessment of patient (caregiver) health literacy and has excellent agreement with the 66-item instrument.[45] It will be used as an exploratory measure.

Caregiver-reported neurobehavioral measures:

- Executive function: The Behavior Rating Inventory of Executive Function (BRIEF) is a parent completed survey of behaviors associated with executive functioning (ability to self-regulate, pay attention and organize, experienced in "real-world" situations) that provides clinically relevant information for evaluating a wide range of behaviors. It has been shown to vary across the range of OSAS severity and to be highly responsive to interventions.[36]
- Behavior: The Child Behavior Checklist (CBCL) is a widely used and validated caregiver-completed survey of behavior that yields standardized, age-adjusted scores on internalizing, externalizing and attentional behavior difficulties for preschool and school-aged children, and is sensitive to the effects of OSA.[46] It complements the BRIEF by assessing a broader range of clinical-behavioral effects of treatment. It is also highly responsive to intervention.[36]
- Attention: The Conners' Third Edition are caregiver questionnaires evaluating symptoms of ADHD that have been shown to be abnormal and improve with treatment in children with OSAS.[36] In combination with the CBCL, it surveys a wider range of behaviors than the primary outcome and thus delineates the fuller spectrum of behavioral change accompanying changes on the primary measure, including ADHD.
- Adaptive behavior: The Caregiver Adaptive Behavior Assessment System, 3rd Edition (ABAS-III) is a caregiver rating of children's everyday functioning, or adaptive behavior, in 3 primary adaptive domains (Conceptual, Social, Practical) that form a single General Adaptive Composite.

- Sleepiness: The Epworth Sleepiness Scale modified for children, to be completed by parental proxy, is a caregiver completed, validated measure of daytime sleepiness that has been used in children with a variety of sleep disorders.[47]
- Self-Efficacy Measure for Sleep Apnea for Caregivers (SEMSA-Caregiver):[48,49]

Sociodemographic factors: Age, race/ethnicity, socioeconomic status (SES), comorbid medical and behavioral health diagnoses, and services that families have in place such as behavioral therapy or applied behavioral analysis (ABA). SES will be defined primarily on maternal education. Family income (which some families may decline to provide), and information on the proportion of families within the family's census track below the poverty level as determined by geocoding each family's address and then linking those to census track and other standardized databases, will be used as ancillary measures of SES.

Health Care Utilization (HCU) Methodology and EMR Surveillance: HCU data will be collected both retrospectively (one year prior to enrollment) and prospectively using interim structured interviews of caregivers (Figure 2) and through ongoing surveillance of electronic medical records (EMR), with adjudication between these sources as needed. We will utilize a query structure to be used by the EMR informatics analytics team for ongoing EMR surveillance for extracting relevant information from inpatient, outpatient and pharmacy records.

Monthly caregiver interviews: As shown on Figure 2, research coordinators will call caregivers on monthly basis on the months with no visits scheduled, to identify adverse events and HCU, including hospitalizations (reason, place and number of days), emergency room visits (reason, place), unscheduled and scheduled medical outpatient visits, and medication prescriptions.

Semi-structured interviews performed by the Mixed Methods Research Lab: We will offer the option for caregivers and subjects to participate in phone interviews to be conducted by MMRL after the 6-month and 12 month visit.

2 COMPLIANCE STATEMENT

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

3 STUDY OBJECTIVES

The overall aim of this proposal is to conduct a randomized controlled trial (RCT) of standard clinical care (SC) compared to a 6-month intensive family-informed intervention (INT) to promote PAP adherence in children with DS and OSAS.

The primary objective of this study is to determine the efficacy of a 6-month intensive behavioral intervention (INT) vs. standard care (SC) in promoting PAP adherence at 6

months after PAP initiation in children with DS and OSAS naïve to PAP or have not used PAP for the past 3 years prior to enrollment. We hypothesize that children receiving INT will show significantly increased objectively-measured PAP adherence at 6 months compared with those receiving SC.

3.1 Secondary Objectives (or Aim)

As a secondary aim, we will evaluate whether the improved adherence is maintained over 12 months. We hypothesize that participants initially randomized to the INT arm will have better adherence at 12 months compared to those in the SC arm.

We will also evaluate the effect of PAP adherence on quality of life, neurobehavioral functioning in children with DS and OSAS. We hypothesize that, irrespective of study arm, increased PAP adherence will be associated with better quality of life, neurobehavioral outcomes.

3.2 Exploratory Objective (or Aim)

Use mixed methods during the randomized controlled trial to identify family perceptions, such as empowerment and self-efficacy, regarding PAP use in youth with OSAS and DS. We hypothesize that INT-PAP will be associated with more positive perceptions compared to SC.

To evaluate the effect of PAP adherence on and healthcare utilization in children with DS and OSAS. We hypothesize that, irrespective of study arm, increased PAP adherence will be associated with reduced healthcare utilization.

Study Endpoints

Primary Outcome Measure:

1.Percentage of Nights Adherent to PAP Therapy from Initiation to 6 Months

PAP adherence will be assessed as the percentage of nights in which the participant is adherent to PAP therapy from initiation (T0) through 6 months (T6). This is calculated as the number of nights meeting adherence criteria divided by the total number of nights during the participant's study participation period, multiplied by 100.

[Time Frame: 6 months]

Secondary Outcome Measures:

Number of Minutes of PAP Use on Nights Used

PAP adherence will be measured as the number of minutes of PAP use per night among nights with any recorded PAP use, calculated per participant from PAP initiation through the end of the 6-month intervention period.

[Time Frame: 6 months]

Change in PedsQL Total Score (Quality of Life)

Quality of life will be measured using the Pediatric Quality of Life Inventory (PedsQL) total score. The PedsQL is a 5-point scale ranging from 0 to 4(0 = Never, 4 = Always), with higher scores indicating better quality of life.

[Time Frame: Baseline, 6 months, and 12 months]

Change in Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) Parent Report Score

Executive functioning will be assessed using the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2), a parent-reported questionnaire that evaluates behaviors associated with executive functioning. Scores are reported as standardized T-scores, with higher scores indicating greater executive dysfunction

[Time Frame: Baseline, 6 months, and 12 months]

Percentage of Nights Adherent to PAP Therapy from Initiation to 12 Months

PAP adherence will be assessed as the percentage of nights in which the participant is adherent to PAP therapy from initiation (T0) through 12 months (T12). This is calculated as the number of nights meeting adherence criteria divided by the total number of days during the participant's study participation period, multiplied by 100.

[Time Frame: 12 months]

4 INVESTIGATIONAL PLAN

4.1 General Schema of Study Design

This will be a randomized controlled 6-month intervention trial. Participants with DS and OSAS will be recruited after clinical referral for PAP initiation (Figure 2). Participants will be contacted by the research team by phone. An explanation of the study will be provided and if interested, a visit will be scheduled to perform informed consent followed by baseline assessments. Participants will then be randomized to a 6-month intensive behavioral intervention (INT) or standard care (SC). Following baseline assessments and randomization, the PAP initiation visit will be scheduled within 2 weeks, but can be scheduled the same day as informed consent and baseline assessments based on family's preference. At the end of the PAP initiation visit, all participants will receive the PAP equipment (e.g., mask, headgear, equipment). All participants will undergo a titration study before the 3-month visit to determine the therapeutic pressure to alleviate OSAS. All participants will complete neurobehavioral testing (NBT) at baseline (T0), 6 (T6), and 12 months (T12) to assess whether PAP adherence and behavioral changes persist after the intervention. Adherence to PAP will be downloaded via modem before every encounter. The Mixed Methods Research Lab at University of Pennsylvania will conduct semi-structured interviews of caregivers and subjects at 6, and 12 months in the group randomized to INT to further expand caregivers’ and subjects’ perceptions of the experience of living with DS and OSAS.

4.1.1 Screening Phase

Potential subjects will be screened using the protocol inclusion and exclusion criteria. 86 children of both sexes and all races and ethnic groups will be recruited from three sites, CHOP,Cincinnati Children's Hospital Medical Center (CCHMC) and University of Miami according to the inclusion and exclusion criteria. Since AT is the first line of treatment of OSAS,[50] we expect that most children would have undergone tonsillectomy, adenoidectomy or a combination of both. However, this is not an inclusion criterion as some children with small tonsils may not have been deemed eligible for AT and /or families may have declined surgery in other cases. Parental/guardian permission (informed consent) will be obtained by the research coordinators prior to any study related procedures being performed. The medical and psychology team will not obtain consent to avoid COI.

4.1.2 Study Treatment Phase (start of the study intervention)

Participants randomized to the SC condition will meet in person or virtually with the physician, nurse and respiratory therapist (RT). It will be a semi-structured visit lasting 60-90 minutes and will include 1) education about a) definition and causes of OSAS, b) importance of treating OSAS and consequences of untreated OSAS, c) use and care of PAP machine, e) how to place mask/headgear and how the caregiver can help, 2) brief demonstration and practice of using the equipment with the child and 3) anticipatory guidance on potential problems (e.g., side effects of PAP, technical and equipment questions, what to do if the child takes it off) and who to call for help. Families will be provided or emailed hand-outs on a) general systematic desensitization procedures (e.g., stepwise exposure to PAP that facilitates habituation), b) importance of bedtime routines, c) recommendations about amounts of sleep for age d) healthy sleep habits, and e) incorporating PAP into family and bedtime routines.

Participants randomized to the INT will have similar PAP initiation, which will be semi-structured and will also last 60-90 minutes and will also include a psychologist. The initiation visit will include following: 1) brief behavioral health assessment to better understand caregiver and patient habits and behaviors, including sleep/sleep routine; 2) education tailored for health literacy of caregiver, including a) definition and causes of OSAS, b) importance of treating OSAS and consequences of untreated OSAS, c) use and care of PAP machine, e) how to place mask/headgear and how the caregiver can help, 3) brief practice and desensitization while demonstrating positive reinforcement, 4) development of systematic desensitization based on clinic observations and experience (e.g., stepwise exposure to PAP that facilitates habituation with a family-tailored and implemented non-food based reward system), 5) incorporating PAP into family and bedtime routines (and if no routines exist, the development of a routine, and 6) anticipatory guidance on potential problems (e.g., side effects of PAP, technical and equipment questions, what to do if the child takes it off) and who to call for help.

4.1.3 Follow-up Phase

The follow-up phase will continue for up to 6 months following the 6 month visit.

4.2 Allocation to Treatment Groups and Blinding

Participants meeting all eligibility criteria will be randomized at the end of the clinical visit for PAP initiation. Randomization will be performed by the Data Coordinating Center (DCC). Participants will be randomized to either INT or SC, at a 1:1 ratio. The coordinator will complete this step in a customized electronic data capture (EDC) system using a standard internet connection that communicates with the secure study portal. After entering key

fields and submitting the web-based forms, eligibility will be electronically ascertained. Upon confirmation, the site staff will be presented with the randomization assignment for that participant. The randomization schema will be setup per the DCC protocol, and stored/maintained by the Brigham and Women's Hospital Program in Sleep Medicine Epidemiology. The randomization distributions and system will be re-assessed on a quarterly basis to ensure that it is working as expected. To minimize problems with connectivity, staff will be asked to confirm internet connectivity and EDC system availability at the beginning of the baseline visit to avoid any potential problems accessing the randomization module. If problems arise with connectivity during a given visit, site staff will be asked to immediately contact the Brigham and Women's Hospital Program in Sleep Medicine Epidemiology to resolve these; a manually generated randomization assignment would then be generated. The DCC will be responsible for providing and documenting appropriate user access to the database, preventing against unauthorized entry into the randomization system. The research coordinator performing neurobehavioral testing will be blinded to the intervention arm.

4.3 Study Duration, Enrollment and Number of Sites

4.3.1 Duration of Study Participation

The participation of each subject will last approximately 1 year after enrollment.

4.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at two investigative sites in the United State, including CHOP CCHMC and University of Miami.

Recruitment will stop when approximately 80 subjects are evaluable.

4.4 Study Population

4.4.1 Inclusion Criteria

1) Males or females ages 6 to 17.9 years of age
2) Diagnosis of Down syndrome/Trisomy 21
3) Clinical referral for PAP initiation to treat OSAS
4) Child naïve to PAP treatment or have not used PAP for the past 3 years prior to enrollment
5) Parental/guardian permission (informed consent)
6) Parent/guardian willing and able to complete behavioral measures and questionnaires.
7) Parent/guardian who comes to study visits must also care for the child at least 4 nights per week.

4.4.2 Exclusion Criteria

1) Child with major illness, such as leukemia or severe cyanotic congenital heart disease listed for cardiac transplant
2) Family planning to move out of the area within the year,

3) Child in foster care
4) Caregivers who do not speak English well enough to complete behavioral and performance measures as most are available and validated only in English.
5) Pregnant or lactating females.
6) Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

5 STUDY PROCEDURES

5.1 Screening/Baseline Visit

Obtain informed consent and confirm further eligibility criteria with caregiver interview (at face-to-face encounter)

- Caregiver rating scales, including the ABAS-III and BRIEF
- Behavioral and Performance testing

Medical Record Review and Data Extraction from electronic medical record (EMR)

Arrange a titration PSG with central scoring.

5.2 Study Treatment Phase

Please see page xii and Figure 1 for details of schedule of intervention and timeline.

5.2.1 Standard Care (SC): Visit 1

Participants in SC will receive usual clinical care (Table 2). Participants randomized to the **SC condition** will meet in person or virtually with the physician, nurse and respiratory therapist (RT). It will be a semi-structured visit lasting 60-90 minutes and will include 1) education about a) definition and causes of OSAS, b) importance of treating OSAS and consequences of untreated OSAS, c) use and care of PAP machine, e) how to place mask/headgear and how the caregiver can help, 2) brief demonstration and practice of using the equipment with the child and 3) anticipatory guidance on potential problems (e.g., side effects of PAP, technical and equipment questions, what to do if the child takes it off) and who to call for help. Families will be provided hand-outs on a) general systematic desensitization procedures (e.g., stepwise exposure to PAP that facilitates habituation), b) importance of bedtime routines, c) recommendations about amounts of sleep for age d) healthy sleep habits, and e) incorporating PAP into family and bedtime routines. At the initiation visit, SC will receive the phone number for the Sleep Clinic nurses and psychologist to call with any questions, for additional support, or to review modem data and make changes to the behavioral plan, but will not have any scheduled contact other than reminder phone calls prior to visits.

5.2.2 Visits 2 and 3

At the three 30-45 minute follow-up visits that will be conducted in person or virtually at months 1 and 3, the PAP device modem will be downloaded and feedback about use of

PAP by the participant will be provided to the family by the medical team; the equipment will be evaluated and a physician or nurse will review any medical concerns, side effects, and adverse reactions. Mask fit will also be assessed. The nurse will provide brief behavioral recommendations if needed, such as reviewing systematic desensitization tasks.

Visit 2 will occur at 1 month following the PAP initiation visit, Visit 3 will occur at 3 months following initiation

- Physical Exam by nurse or physician
- Check of skin, nasal, eye irritation
- Check fit of the mask and headgear
- Equipment Check
- Review of Use and Cleaning of Equipment
- Modem download of objective adherence data
    - Feedback about adherence will be reviewed
    - Strategies to improve adherence will be discussed by nurse and RT
- Assess possible adverse events
- Medical History and Record Review

5.2.3 Visit 4

Visit 4 will occur at 6 months following the PAP initiation visit and will last about 60-90 minutes. Visit 4 will include a 30 minute follow-up visit during which the PAP device will be downloaded and feedback about use of PAP by the participant will be provided to the family by the medical team; the equipment will be evaluated and a physician or nurse will review any medical concerns, side effects, and adverse reactions. Mask fit will also be assessed. The nurse will provide brief behavioral recommendations if needed, such as reviewing systematic desensitization tasks. Neurobehavioral assessments and caregiver questionnaires will also be administered.

- Caregiver rating scales, including the ABAS-III and BRIEF
- Behavioral and Performance testing
- Physical Exam by nurse or physician
- Check of skin, nasal, eye irritation
- Check fit of the mask and headgear

- Equipment Check
- Review of Use and Cleaning of Equipment
- Modem download of objective adherence data
    - Feedback about adherence will be reviewed
    - Strategies to improve adherence will be discussed by nurse and RT
- Assess possible adverse events
- Medical History and Record Review
- Transition to clinical care

5.2.4 INT intervention: Visit 1

Participants randomized to the INT will have a PAP initiation visit, which will be semi-structured and will also last 60-90 minutes and will also include the physician, nurse, RT and a psychologist either in person or virtually. The initiation visit will include following: 1) brief behavioral health assessment to better understand caregiver and patient habits and behaviors, including sleep/sleep routine; 2) education tailored for health literacy of caregiver, including a) definition and causes of OSAS, b) importance of treating OSAS and consequences of untreated OSAS, c) use and care of PAP machine, e) how to place mask/headgear and how the caregiver can help, 3) brief practice and desensitization while demonstrating positive reinforcement, 4) development of systematic desensitization based on observations and experience (e.g., stepwise exposure to PAP that facilitates habituation with a family-tailored and implemented non-food based reward system), 5) incorporating PAP into family and bedtime routines (and if no routines exist, the development of a routine, and 6) anticipatory guidance on potential problems (e.g., side effects of PAP, technical and equipment questions, what to do if the child takes it off) and who to call for help.

5.2.5 Visits 2 and 3

After the initiation visit (Visit 1), INT will have “face-to-face” visits either in person or virtually at months 1, 3 and 6, and phone calls and visits with the PAP psychologist and team (Table 2.) This structure will be influenced and may change based on information and feedback obtained from the qualitative portion of this application (R61). Follow up visits will last about 30-45 minutes. At each visit, PAP adherence will be downloaded from the modem and reviewed, problem solving and a further behavioral plan will be discussed, questions/concerns will be addressed, equipment will be checked and the physician investigator will systematically review medical concerns and side-effects. The mask fit will also be assessed. The psychologist will review progress based on downloads; discuss strategies to optimize adherence, tailored to the family and youth’s needs; and discuss contingency rewards that encourages families not to use food as a reward but other reinforcing motivators based on adherence to goals of each family. Phone calls will be made for continued engagement, review of downloads and retention, as well as to provide external accountability, problem solving, and reinforcement. In addition, text messages will be sent to caregivers as determined by the qualitative part of the study, to remind them about PAP use and to maintain a positive outlook regarding PAP.

Visit 2 will occur at 1 month following the PAP initiation visit and Visit 3 will occur at 3 months following initiation

- Physical Exam by nurse or physician
- Check of skin, nasal, eye irritation
- Check fit of the mask and headgear
- Equipment Check
- Review of Use and Cleaning of Equipment
- Modem download of objective adherence data
    - Feedback about adherence will be reviewed
    - Strategies to improve adherence and changes to the behavioral plan will be discussed by psychologist
- Assess possible adverse events
- Medical History and Record Review

5.2.6 Visit 4

Visit 4 will occur at 6 months following the PAP initiation visit and will last about 60-90 minutes. Visit 4 will include a 30 minute follow-up visits either in person or virtually during which the PAP device will be downloaded and feedback about use of PAP by the participant will be provided to the family by the psychologist; the equipment will be checked and a physician or nurse will review any medical concerns, side effects, and adverse reactions. Mask fit will also be assessed. The psychologist will provide behavioral recommendations if needed. Neurobehavioral assessments and caregiver questionnaires will also be administered.

- Caregiver rating scales
- Behavioral and Performance testing
- Physical Exam by nurse or physician
- Check of skin, nasal, eye irritation
- Check fit of the mask and headgear
- Equipment Check
- Review of Use and Cleaning of Equipment
- Modem download of objective adherence data

- Feedback about adherence will be reviewed
- Strategies to improve adherence and changes to the behavioral plan will be discussed by psychologist

- Assess possible adverse events
- Medical History and Record Review
- Semi-structured interview (INT) group
- Transition to clinical care

5.2.7 Phone Calls

In the INT, participants will receive phone follow up from the psychologist at weeks 1, 2, 6, 8, 10, 14, and 20. These phone calls may last 5-15 minutes, depending on how well the family is doing and the support that they may require.

In the SC, participants will be provided the number for the psychologist and medical team should they have questions or need support in implementing PAP.

For all phone calls with the psychologist, the psychologist will assess the family's report of progress, review objective adherence data obtained from the modem and discuss with family, identify barriers or problems for use, offer support and encouragement, and change the behavioral plan based on progress. Should medical or equipment concerns arise during calls, the psychologist will route those messages along to the study nurse who will follow up with the family.

For both groups, the research coordinator will make monthly phone calls, starting at month 2 through month 11 for retention, healthcare utilization assessment (e.g., illnesses, doctor visits, emergency department visits, hospitalizations, and scheduling of visits.

5.2.8 Overnight Titration Polysomnogram

The titration polysomnography (PSG) will be performed as part of research unless clinically indicated between the 1 month and 3 month visits. PSGs will be performed in a dedicated pediatric sleep laboratory as previously described[34]. The following parameters will be determined using standard pediatric techniques and scoring:[35] sleep architecture, respiratory events, arterial oxygen saturation (SpO2), end-tidal carbon dioxide tension (ETCO2), and optimal positive airway pressure. Studies will be interpreted by the Data Coordinating Center, located in Boston, MA and results reported to sites.

Existing laboratory equipment will be used, but data will be standardized by using the same montage and similar sensors, sampling rates and filters. Participants will report to the sleep laboratory 1 hour before their usual bedtime and remain at the sleep laboratory in a quiet dark room until the study ends the following morning at their spontaneous wake time. Children must be accompanied by at least one parent/guardian during the night. Weekend slots will be made available, as feasible, to families to facilitate recruitment. The completed

PSG will be exported after removing the child' name and identifying information (other than date of study) as a standardized European Data Format (EDF) file and electronically transmitted to an FTP server at the central Sleep Reading Center (at Brigham and Women's Hospital) for standardized scoring. The following are monitored: Sleep architecture (6 EEG sites [F3/M2, F4/M1, C3/M2, C4/M1, O1/M2, O2/M1], bilateral electro-oculograms [EOG: ROC/A2, LOC/A1], submental electromyography [EMG]; airflow by oronasal thermocouple; nasal pressure cannula; snoring sound; respiratory effort (chest and abdominal wall inductive plethysmography); end-tidal CO2 (capnography waveform and numeric display); pulse oximetry (numeric and plethysmograph waveform in the 2 sec averaging mode); ECG with a standard 3-lead precordial placement; leg movements (bilateral tibial EMG); body position. Studies will be scored using standard pediatric techniques and scoring.[51,52]

5.2.9 Visit 5

Visit 5 will occur 1 year following the PAP initiation visit for all participants.

- Caregiver rating scales
- Behavioral and Performance testing
- Modem download of objective adherence data
- Assess possible adverse events
- Medical History and Record Review
- Semi-structured interview (INT) group

5.2.10 TABLE OF INTERVENTION VISITS

Table 2: Intervention Visit schedule. Visits are shown in Table 2. Participants in both arms will have the same initiation visit, plus a CPAP titration PSG within 1 month to determine the therapeutic pressure to alleviate their OSAS.

	SC	**INT**
Initiation	X	X
Titration PSG	X	X
Follow-up visits	**3 face-to-face visits either in person or virtually at** 1,3, and 6 months	**3 face-to-face visits either in person or virtually** at months 1, 3, and 6 months
Phone calls	Family initiated phone calls. They have the phone number of nurse and psychologist to call as needed. Will be provided the phone number of the medical research team to call with	**Telehealth Calls by psychologist** at weeks 1, 2, 6, 8, 10, 14, and 20 Will be provided the phone number of the medical research team and the psychologist call with questions or concerns at any time during the study.

	questions or concerns at any time during the study.	
		Texts
Retention calls from coordinator monthly from months 6-12.		Retention calls from coordinator monthly from months 6-12.

5.3 Follow-up Phase

The research coordinator will contact the family by phone at months 7, 8, 9, 10, and 11 for retention and to inquire about healthcare utilization, and adverse events.

5.3.1 Visit 6: End of Study

All participants will return at month 12 final visit, which will include questionnaires, neurobehavioral assessments, health care utilization, adverse events, adherence, and semi-structured interviews. This visit will be conducted in person or virtually, with the exception of the neurobehavioral performance tasks (e.g., Go-No-Go Continuous Performance Task and Pegboard0, which must be completed in person.

5.3.2 Unscheduled Visits

Due to the nature of the study and frequent follow up by phone, unscheduled visits are not expected. Should participants and families require medical intervention related to PAP (for example, skin or nasal irritation), they will contact the study nurse. For all other medical concerns, they will be referred to their primary care team.

5.4 Concomitant Medication

All prior and concomitant medications used within 1 month prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

5.5 Subject Completion/Withdrawal

5.5.1 Discontinuation of Assessment Tasks

- Neurobehavioral Assessments
  - Children and families are free not to answer any questions to which they object.
  - Study staff have clinical expertise in evaluating children with DS, and if children are exhibiting frustration or fatigue, families will be given the option to stop the assessments.
    - Study staff will complete a structured appraisal form for each testing session that rates the ability of children to complete each task, including information on why a child was unable to complete the task (e.g., ability to understand task, visual/motor delays, etc.)
  - Children will not be withdrawn from the study, should they not complete the neurobehavioral tasks.
  - Measures used in the study are standard for medical or psychological evaluations, and therefore, they have minimal risk associated their administration.

5.5.2 Study Discontinuation and Participant Discontinuation/Withdrawal

Participants are free to withdraw from participation in the study at any time upon request without prejudice to their care.

Participants may also be discontinued from the study at the discretion of the Investigator for lack of adherence to visit schedules or AEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

The reason for participant discontinuation or withdrawal from the study will be recorded in a Note to File attached to the participant's study file. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced by a new study participant.

5.5.2 Early Termination Study Visit

Subjects who withdraw from the study will have as many procedures as possible carried out for the Endpoint Visit at the early termination visit, which may include sending questionnaires home to the family or a link for them to be filled out if the family is unable to come in for a visit.

5.6 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for one of his or her scheduled visits, and is unable to be contacted by the study site staff.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the time frame allotted for the specific point of the study's timeline. The site will counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the study coordinator will make every effort to regain contact with the participant (where possible, 3 telephone calls, email, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

  Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up which will be documented as a Note to File.

6 STUDY EVALUATIONS AND MEASUREMENTS

6.1 Screening and Monitoring Evaluations and Measurements

6.1.1 Medical Record Review

- Date of birth

- Sex
- Race
- ZIP code
- Medical History
- Healthcare utilization 1 year prior to enrollment and throughout the study.

6.1.2 Physical Examination

Demographics, medical and psychosocial history will be reviewed with caregiver. The participant will be fit for a PAP mask by the study nurse.

6.1.3 Other Evaluations, Measures

Neurobehavioral Testing (NBT): Behavioral performance testing will take place in person and will take approximately 40 minutes for the child to complete. Caregiver questionnaire completion will take approximately 90 minutes and may be completed during the visit or virtually. Testing will be administered by a trained Research Coordinator who has been specifically trained in assessments with this population. Tests will be performed in the same order across visits. Testing will be performed in a private, quiet room with adequate lighting and table space. Breaks are built into the testing sequence to avoid excess fatigue. Trained test administrators will complete a structured appraisal form for each testing session that describes the ability of children to complete each task, including any behavioral difficulties (e.g., ability to understand task, visual/motor delays, behaviorally non-compliant, verbal ability, verbal refusal, acquiescence, etc.) Such information will be critically important in developing the testing battery for future RCTs. The parent will complete the questionnaires on the SLICE data management system, as well as data entry directly to the questionnaires websites in a separate room, when possible, while their child is being tested. All tests will be performed as outlined in the Neurobehavioral Testing MOP. The Research Coordinator will be available for assistance, and will ensure completion of all tests at the end of the session.

Some neurobehavioral measures utilize a date stamp when questionnaires are entered into the commercial data entry and scoring websites. Some websites also require date of birth as well to be entered to assure the proper version is used according to the child's age.

Two tests will be performed by the children:

- 9-Hole Pegboard
- Go No-Go tests, early childhood version

Children with DS tend to do best on tasks that are more concrete and can be easily visualized and both tasks meet these requirements. As we recognize that some young children with DS may find these tasks challenging, we will slightly modify procedures for introducing these tasks to optimize engagement. Examples will include opportunities to pick up and place pegs prior to beginning the pegboard task, and practice in pressing the button to examine signals prior to beginning the Go No Go task.
Because children with DS may have shorter attention spans than typically developing children, we will administer only the early childhood version of the Go No Go task. These modifications will help ensure maximal engagement of the children in the testing and allow

us to obtain additional information on the performance of any children who are unable to complete the tasks.

Objective Performance Tests:

- *Vigilance:* The Go-No-Go Continuous Performance Task[38] will provide an objective measure of sustained attention (vigilance), which is considered a fundamental factor influencing executive functioning and behavior. The computerized Go-No-Go will allow us to assess whether observed changes in behavior are accompanied by objectively measured changes in attentional abilities. The test is easy to administer and appropriate for children as young as 3 years. In this task, children are presented with pictures of colored fish and sharks and asked to respond to only the fish using a button box.
- *Fine motor coordination:* The NIH Toolbox 9-Hole Pegboard Dexterity Test is a test of fine motor coordination that has been shown to be abnormal in adults[39,40] and children[36] with OSAS.

Caregiver rating scales and their constructs. The following scales will be used:

Quality of life and symptoms:

- Generic Quality of life: The Pediatric Quality of Life Inventory (PedsQL) is a well-validated, generic measure of global quality of life that will be obtained by caregiver proxy and has been used in children with DS.[32]
- Disease-specific quality of life: The OSAS-18 is a validated caregiver questionnaire comprising assessments of SDB symptoms and disease-specific quality of life that has been shown to improve after OSA treatment.[41]
- OSA symptoms: The caregiver-completed Pediatric Sleep Questionnaire (PSQ) is the most validated questionnaire assessing OSA symptoms.[42]
- Pediatric sleep disorders: The Children's Sleep Habits Questions (CSHQ) is a well-validated screener across multiple domains of common sleep disorders in children.[43]

Family functioning measures:

- Family Assessment Device, a survey of 7 domains of family functioning, including aspects such as problem solving and communications.[44]
- Parenting Style Questionnaire, a survey of the type of parenting style (authoritative, authoritarian or permissive).
- Parenting Stress Index Short Form, an assessment of parents' perception of stress in the parent-child system.
- Rapid Estimate of Adult Literacy in Medicine - Short Form, a 7-item word recognition test that provides a rapid assessment of patient (caregiver) health literacy and has excellent agreement with the 66-item instrument.[45] It will be used as an exploratory measure.

Caregiver-reported neurobehavioral measures:

- Executive function: The Behavior Rating Inventory of Executive Function (BRIEF) is a parent completed survey of behaviors associated with executive functioning (ability to self-regulate, pay attention and organize, experienced in "real-world" situations) that provides clinically relevant information for evaluating a wide range of behaviors. It has been shown to vary across the range of OSAS severity and to be highly responsive to interventions.[36]
- Behavior: The Child Behavior Checklist (CBCL) is a widely used and validated caregiver-completed survey of behavior that yields standardized, age-adjusted scores on internalizing, externalizing and attentional behavior difficulties for preschool and school-aged children, and is sensitive to the effects of OSA.[46] It complements the BRIEF by

assessing a broader range of clinical-behavioral effects of treatment. It is also highly responsive to intervention.[36]

- Attention: The Conners' Third Edition are caregiver questionnaires evaluating symptoms of ADHD that have been shown to be abnormal and improve with treatment in children with OSAS.[36] In combination with the CBCL, it surveys a wider range of behaviors than the primary outcome and thus delineates the fuller spectrum of behavioral change accompanying changes on the primary measure, including ADHD.
- Adaptive behavior: The Caregiver Adaptive Behavior Assessment System, 3rd Edition (ABAS-III) is a caregiver rating of children's everyday functioning, or adaptive behavior, in 3 primary adaptive domains (Conceptual, Social, Practical) that form a single General Adaptive Composite.
- Sleepiness: The Epworth Sleepiness Scale modified for children, to be completed by parental proxy, is a caregiver completed, validated measure of daytime sleepiness that has been used in children with a variety of sleep disorders.[47]

Sociodemographic factors: Age, race/ethnicity, socioeconomic status (SES), comorbid medical and behavioral health diagnoses, and services that families have in place such as behavioral therapy or applied behavioral analysis (ABA). SES will be defined primarily on maternal education. Family income (which some families may decline to provide), and information on the proportion of families within the family's census track below the poverty level as determined by geocoding each family's address and then linking those to census track and other standardized databases, will be used as ancillary measures of SES.

Health Care Utilization (HCU) Methodology and EMR Surveillance: HCU data will be collected both retrospectively (one year prior to enrollment) and prospectively using interim structured interviews of caregivers (Figure 2) and through ongoing surveillance of electronic medical records (EMR), with adjudication between these sources as needed. We will utilize a query structure to be used by the EMR informatics analytics team for ongoing EMR surveillance for extracting relevant information from inpatient, outpatient and pharmacy records.

Monthly caregiver interviews: As shown on Figure 2, research coordinators will call caregivers on monthly basis on the months with no visits scheduled, to identify adverse events and HCU, including hospitalizations (reason, place and number of days), emergency room visits (reason, place), unscheduled and scheduled medical outpatient visits, and medication prescriptions.

Semi-structured interviews performed by the Mixed Methods Research Lab (MMRL): We will offer the option for caregivers and subjects to participate in phone interviews to be conducted by MMRL after the 6-month and 12 month visit. Semi-structured interviews will explore such key constructs as knowledge/belief about OSAS and PAP therapy, routines and resources that promote or limit PAP use, barriers, self-efficacy, and communication and attitudes about PAP. Grounded by Consolidated Framework for Implementation Research (CFIR), the focus will also be on identifying the multiple factors necessary to maximize the implementation of appropriate, acceptable, feasible, and high-fidelity interventions for implementation and adherence to PAP in pediatric patients diagnosed with DS and OSAS. Five additional domains that will be explored include 1) the characteristics of the intervention itself, 2) the outer setting, including external policies and market factors, 3) the inner setting, including practice structural characteristics, culture, climate, openness to change and communication patterns, 4) the characteristics of the individuals involved, and 5) the process by which the intervention is adopted and maintained.

6.2 Safety Evaluation and Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Subject safety will be monitored by adverse events, physical examinations, and caregiver report. Toshihiro Imamura, MD has been appointed as independent safety monitor for both sites. Dr. Toshihiro is a sleep medicine attending physician at Children's Hospital of Philadelphia. Dr. Toshihiro Imamura will assess the potential appearance of COI between the participant's medical team and the investigative team. In addition, she will review safety data every 6 months or more frequently if adverse events are reported.

- Clinical monitoring will be carried out day-to-day by the site clinicians under the supervision of the investigators. This monitoring will follow DSMB policies, and will include oversight of the project's performance, safety, treatment, and stopping rules. The DSMB will review the information collected by the site's clinicians every 6 months, calling an emergency meeting in the event of a serious adverse event.

7 STATISTICAL CONSIDERATIONS

General Statistical Analysis Considerations: Demographic and baseline characteristics and outcomes will be summarized with descriptive statistics. Histograms and one-sample Kolmogorov-Smirnov tests will be used to determine normalcy of distribution. For seriously skewed data, transformations (e.g., logarithmic) may be applied to the data prior to analysis. Depending upon distribution and ability to normalize skewed data, appropriate parametric or nonparametric procedures will be used. Linear mixed effects models will be use to analyze correlated data, such as PAP adherence, QOL and neurobehavioral measures.[53,54] Stata 13.0 will be used for analysis with two-sided tests and a p-value < 0.05 as the criterion for statistical significance.

Data Sharing Plan: The Data Coordinating Center (DCC) will manage the data. Data will be uploaded to the National Sleep Research Resource (sleepdata.org), a NHLBI-funded resource. This is a web accessible portal and tool resource designed to facilitate sharing of large amounts of data through cloud computing and open-source tools for visualizing and analyzing varied data and will provide a rich repository for sharing the study data with the scientific community.

7.1 Primary Endpoint

Measurement of PAP adherence from PAP initiation (T0) to the end of the 6-month intervention (T6) between the 2 arms based on intention to treat. PAP adherence will be expressed as percentage of nights used, and minutes of use on nights used during this 6-month period. This will be first tested with a two-sample t-test if the data are normally distributed, and the Wilcoxon rank sum test if not. PAP predictive factors for adherence at 6 months will be evaluated by multiple linear regressions, including possible confounding factors, some of which may be identified during the R61 phase of this proposal. The distribution of the outcome variable will be assessed visually and statistically, and transformation can be applied to meet the normality assumption required by linear

regression. Stepwise model selection algorithm may be applied to help determine the final model.

7.2 Secondary Endpoint

- Measurement of PAP adherence from the end of the 6-month intervention (T6) to 12 months after initiation (T6 to T12) between the 2 arms. This will allow us to evaluate the effect of the intervention 6 months after the end of the intervention. PAP adherence will be defined the same way as in T0-T6 period. Similarly, this will be tested with a t-test or Wilcoxon rank sum test as appropriate, and potential PAP factors associated with adherence from T6-T12 will be evaluated by multiple linear regressions. We are also interested in assessing whether the improved adherence is maintained over 12 months within each arm using a paired t-test or its nonparametric equivalent as appropriate to compare the adherence in T0-T6 to that of T6-T12 separately for each arm. We will also perform a linear mixed-effects model for each arm on the adherence in the two time periods, adjusted for covariates of the interest. In this model, the time period will be the independent variable, e.g., 0 for T0-T6 and 1 for T6-T12, and we test whether the slope of time differs from 0. This model accounts for within-subject correlation due to repeated measures by including a subject-specific random effect. In addition, we would like to evaluate whether INT group maintains a better adherence as compared to SC group. To test this hypothesis, we will similarly perform a linear mixed-effects regression but for all subjects with an interaction term of time x group, adjusted for baseline adherence (i.e., adherence in T6-T12) and other covariates of interest. Testing this interaction term will tell us whether one arm maintains a better adherence than the other arm over the 12 months period.

Quality of life (QOL) and neurobehavioral changes between the 2 arms at baseline (T0), at the end of the 6-month intervention (T6), and 6 months after the end of the intervention (T12), respectively will be tested with a t-test if the data are normally distributed, and the Mann-Whitney-Wilcoxon test if not. One-way ANOVA will be utilized to test differences in QOL and neurobehavioral outcomes within groups at 0, 6, and 12 months if data are normally distributed. If not, one-way ANOVA on ranks will be utilized. Longitudinal models using generalized estimating equations (GEE) will be fitted to explore effects of randomization on QOL and neurobehavioral changes. An indicator variable for randomization, time, and a time by randomization group interaction term will be included in the models. If the interaction term differs significantly from zero, this will indicate that the change over time in the outcome of interest differs significantly between the two arms. In the longitudinal model using GEE to assess the intervention effect on the QOL and neurobehavioral outcomes over time, we will include the PAP adherence as well as an interaction of group by adherence, where the PAP adherence is measured as percentage of nights used and minutes of use on nights used. By testing these interaction terms, we will be able to determine whether the intervention effect on the outcomes is modified by the adherence level. We will assess the sensitivity of results to the choice of working correlation structure that models association in the GEE analyses. We will also implement quasi-least squares (QLS), an approach based on GEE that allows for implementation of the Markov correlation structure[55]. The Markov structure is plausible if participants have unequal temporal spacing of their measurements. In addition, we will consider the application of mixed effects models if the assumptions of these models are met. The baseline obstructive apnea hypopnea index will be included in the model, and potential confounding variables

such as age, gender, race, socio-economic status and BMI will also be included in the models.

Mixed Methods Outcome: Coded data will be summarized, examined for patterns and used to identify factors associated with adherence and non-adherence as well as implementation. Data between the 2 randomization arms will be compared.

7.3 Statistical Methods

7.3.1 Baseline Data

Demographic and baseline characteristics and outcomes will be summarized with descriptive statistics. Histograms and one-sample Kolmogorov-Smirnov tests will be used to determine normalcy of distribution. For seriously skewed data, transformations (e.g., logarithmic) may be applied to the data prior to analysis. Depending upon distribution and ability to normalize skewed data, appropriate parametric or nonparametric procedures will be used.

7.4 Sample Size and Power

A sample size of 80 participants evaluable at the end of the study, 40 randomized to SC and 40 to INT, will have 80% power to detect a moderate effect size of 0.64 using a two group t-test with a 0.05 two-sided significance level. By convention, a Cohen's d effect size[56] 1 of 0.2 to 0.3 is considered to be a small effect, 0.5 would be considered a medium effect, and 0.8 or larger would be a large effect. Thus, our effect size of 0.64 would be a medium effect. We plan to enroll 86 participants to account for 7% attrition.

Primary Outcome: Determine the efficacy of INT-PAP vs. SC in promoting PAP adherence:

- Based on our preliminary data, the average percentage of nights used during the first 6 months following initiation is 42% in youth with DS. The proposed sample size of 80 evaluable participants will allow us to detect an increase of 13% with 80% of power between SC and INT at 6 months.
- Based on our preliminary data, the average minutes of PAP use on nights used during the first 6 months following initiation is 126 in youth with DS. The proposed sample size of 80 evaluable participants will allow us to detect an increase of 30 minutes with 80% of power between SC and INT at 6 months.

Secondary Outcome: Evaluate the effect of PAP adherence on quality of life (QOL) and neurobehavioral outcomes:

- In our preliminary data of QOL in children with DS[32] the mean caregiver-reported Total QOL was 68.1+13.8. We expect to detect a difference of 10 in the PedsQL score between the control and intervention groups at 6 months that will result in an effect size of 0.714. This effect size requires a total sample size of 64 (32 in each arm) to achieve 80% power at significance level of 0.05. We expect there will be 80 participants evaluable at the end of the study to ensure adequate power and account for possible deviations from published data.

- Based on data by co-investigator Esbensen et al[57], mean executive functioning at baseline in children with DS measured by the Behavior Rating Inventory of

Executive Function (BRIEF) is 60 ± 12. The proposed sample size of 80 evaluable participants will allow us to detect a difference on 7.5 points with 80% of power between SC and INT at 6 months.

8 SAFETY MANAGEMENT

Toshihiro Imamura, MD will be the independent safety monitor for both sites. He is based at Children's Hospital of Philadelphia. Dr. Toshihiro Imamura will assess the potential appearance of COI between the participant's medical team and the investigative team. In addition, she will review safety data every 6 months or more frequently if adverse events are reported.

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or

- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting must be consistent with regulatory, sponsor or GCRC requirements (if applicable)

8.7 Medical Emergencies

Conditions that will generate an Urgent Medical Referral Alert are those laboratory, physiological or behavioral findings that are believed to represent conditions that may require additional evaluation by the participant's health care providers in a timely manner.

8.7.1 Suicidal ideation

It should be noted that if any of these conditions occur after enrollment (i.e., not during a screening visit that disqualifies the child from enrolling in the study), these conditions will also be reported as Adverse Events.

An Urgent Medical Referral Alert should be completed and the site PI notified within 24 hours of first knowledge of the event.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

Randomization will be performed by the Data Coordinating Center. Participants will be randomized to either INT or SC, at a 1:1 ratio.

9.1.2 Blinding

The trained research coordinator performing neurobehavioral testing will be blinded to the intervention arm.

9.2 Data Collection and Management

The CRF is the primary data collection instrument for the study and all data requested on the CRF must be recorded. Samples of each form are provided online with direct "point of care" data entry via the Data Management System (Slice), as well as PDF copies available for print at the study portal. Study-designated personnel from each site will be trained in Case Report Form completion and entry into the Data Management System. Validation checks will be performed at the centralized database to verify data accuracy and identify missing, unclear, illogical, or problematic responses. Queries will be generated to resolve discrepancies.

Every effort will be made to have parents complete all questionnaires during an in person visit. However, in the event that a parent has limited availability for in person visits, parents will be provided with alternate methods to complete these questionnaires. We plan to provide families with paper forms that can be mailed or emailed back to the study coordinator. Coordinators will instruct the parent not to provide any personal identifiers on paper forms and the RC will check the forms for PHI and remove any if found. Families will also be given the opportunity to complete these questionnaires electronically. An email link to the SLICE data management system will be sent to parents for remote completion of neuro-behavioral forms. SLICE is managed by The DCC. The SLICE Data Management

system has a safeguard that will not allow parents to enter PHI directly into the system. CBCL for children 6 years and older, the only measure that assess for suicidal ideation, will be completed during an in person visit only. These alternatives are critical to have a complete dataset in all participants.

The Data Management System (SLICE) assures confidentiality via encryption and password protection. PDF copies can be printed for backing up the data. These will be stored in a locked cabined in a restricted access room. Data will be stored indefinitely after study completion.

At the completion of the study, de-identified study data will be deposited in NHLBI's data repositories, including BioLINCC and the National Sleep Research Resource to support future research and education. All PHI will be removed. Access to these data will be controlled and require approve data use agreements and other applicable regulatory approvals.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Data will be saved in the Data Management System (SLICE) similar to IRB 14-011214. No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

NHLBI will establish an external DSMB according to NHLBI policies if needed. We anticipate that members will include experts in pediatric sleep-disordered breathing, Down syndrome, biostatistics, and clinical trials (some overlapping). The DSMB will convene to review the final protocol and DSMB Charter before study initiation and then periodically, and not less frequently than annually either in person or via teleconference. The DSMB Chair will receive all reports of serious adverse and unexpected adverse events and treatment failures in real time. The DSMB also will receive interim reports on a monthly to quarterly basis (according to their preference.) The Data Coordinating Center will be responsible for assembling materials/reports for the DSMB and NIH and maintaining all regulatory files across the duration of the study.

Each site-PI will be primarily responsible for overseeing safety at his/her site. Safety monitoring will include careful assessment and appropriate reporting of adverse events (AEs) as indicated below and will also include a regular assessment of the number and type of serious AEs (SAEs). Any SAE that might reasonably be due to the study intervention will be reported to the local IRB, CHPS and NIH within 24 hours of its occurrence.

Definitions: Adverse Events, Serious Adverse Events, Urgent Medical Referrals, and Treatment Failures: Definitions and Reporting Approaches

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings or abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event. An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs during a participant's enrollment period in the study including the clinically significant worsening of an already existing symptom, physical sign and abnormal laboratory value, whether or not the event is considered to be related to the study or the intervention under investigation. Preexisting diseases or conditions present or detected at the start of a study that do not worsen including any day-to-day fluctuations or anticipated day-to-day fluctuations will not be captured as Adverse Events (AE), including those identified as expected in high frequency and as defined in the protocol.
Expected Adverse Events:
Adverse events that are expected and are identified in the protocol and for the purpose of this study have been identified as:

• Foreseeable (expected) mild adverse events that may not warrant reporting
• Foreseeable (expected) adverse events that exceed threshold definitions and warrant reporting

Unexpected Adverse Events
Adverse events that are not expected and not identified in the protocol or consent form. Adverse Events in this category will be reported.

Serious Adverse Events (SAE)
Any event that is life threatening or fatal; results in significant or persistent disability; requires hospitalization or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. An SAE Form must be completed for all events in this category according to the guidelines listed in the Manual of Procedures.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study follow-up. For this study, the study treatment follow-up is defined as the last scheduled visit.

Recording and Reporting Adverse Events
At each contact with the subject, the research coordinator will seek information on AEs by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate AE module of the case report form (CRF).

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. The following data will be recorded:

• Any event reported by the participant or parent, other than those expected and identified in the protocol to the site PI.

• Signs and Symptoms will be graded by the Research Coordinator utilizing a 5-grade scale as listed in a manual of procedures.

• Each event will be assessed by the Principal Investigator (PI) for its relationship to study participation according to the guidelines listed in a Manual of Procedures.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless it is surgery occurring as the assigned treatment. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event if it occurred for a diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

Follow Up of Adverse Events
The research coordinator will follow every AE to a satisfactory outcome or stabilization of the event, even when this requires a time period beyond the scope of the study. The coordinator will record each AE outcome on the case report form according to the instructions outlined in a Manual of Procedures. SAEs that are ongoing at the end of the study period must be followed to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Post-study Adverse Event Follow Up
All unresolved adverse events should be followed until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the coordinator should instruct each participant and parent(s) to report any subsequent event(s) that they believe may be related to participation in this study.

Time for Reporting of Serious Adverse Events
The clinical site is responsible for reporting SAEs to the DCC within 24 hours of first knowledge of the event via telephone, followed by completion of the corresponding case report form within 48 hours. The investigator will keep a copy of the SAE form on file at the study site. Within the following 48 hours, the investigator must provide further information on the SAE in the form of a written narrative. This should include a copy of the completed SAE form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the DCC. In addition, the site must promptly report all SAEs to their IRB via written, dated notification in accordance with the IRB’s reporting requirements. Copies of all such correspondence must be maintained in the clinical site’s regulatory binder.

Treatment Failure
Currently, there are no guidelines for what is considered a therapeutic effect of CPAP on physical or neurobehavioral health in children. While all participants who receive a device and attend the first initiation visit will be included in the primary analysis, an intervention failure would be identified as any child who uses the CPAP device less than or equal to an average of 2 hours/week at the 6-month assessment visit for the 1 month prior to the 6-month visit.

ClinicalTrials.gov

The study will be registered in ClinicalTrials.gov

9.4.2 Risk Assessment

Medical history, interviews and record reviews: As with any study that involves collecting data, it is possible that someone who is not involved with the study may get access to participants' confidential information. Every precaution will be taken to secure participants' personal information to ensure confidentiality. At the time of participation, each participant will be assigned a study identification number. This number will be used on data collection forms and in the study database instead of names and other private information. A separate list that links each participant's name to the study identification number will be maintained for future reference and communication.

Physical exam: Participants may experience momentary embarrassment or discomfort, but this is unlikely. This brief exam is similar to exams that children normally have as part of their regular medical care.

Neurobehavioral Testing: Not greater than minimal risk. This testing is potentially stressful or anxiety-producing; these risks will be addressed by offering breaks from testing as needed and having examiners who are well-trained in testing children and adolescents, taking into account possible developmental delays in study participants. Testing will be conducted in an appealing and quiet private area with child-sized furniture. Administration manuals for the neuropsychological assessments will be utilized at both site to standardize testing. Staff administering testing have received training on administering assessments in a standardized manner and supporting kids with DS and managing behaviors/encouragement. They will complete a rating of the child's performance consistent with prior NIH-funded studies of children with DS. (e.g., U01 HL125295-S1: Sleep for Children with DS).

If at any time during the assessment there is concern that a participant is reported by his/her parent/caregiver to have suicidal ideation, the study team will immediately evaluate the participant. The Neurobehavioral Subcommittee has developed a plan for suicidal ideation and suspected child abuse. Each site has modified this to specify local individuals and mechanisms for referral. All site-specific plans identify the primary professionals who will be contacted in the event of suicidal ideation or suspected child abuse, as well as backups when the primary is unavailable. These professionals will be responsible for contacting and working with local mental health staff. All sites also identify the local department that participants will be escorted to by study staff in the event that the primary and backup professionals cannot be contacted.

Polysomnography: Not greater than minimal risk. No significant risks are encountered from polysomnography, which is a standard, noninvasive monitoring procedure. Sleeping away from home may be unsettling. To allay anxiety, the subject's parents/guardians will be allowed to stay overnight in the same room as the subject. The subjects may develop skin rashes as a result of adhesive tapes.

9.4.3 Potential Benefits of Trial Participation

The risks of this study are not greater than minimal. Participation in the study may not benefit participants directly. Children may benefit from being screened for this study, and improving PAP adherence. Any data indicating a health risk will be made available to the participant's primary care provider as soon as those data are reviewed. The information obtained from this study will improve our understanding of the experience of living with DS, the effects of a behavioral intervention in promoting PAP adherence in children with DS and OSAS. These will ultimately lead to better holistic management of children with DS and OSAS. Participants and their families may benefit from knowing that they will contribute to a clinical research study that is important to the health of individuals with DS.

9.4.4 Risk-Benefit Assessment

The information obtained from this study will improve our understanding of the experience of living with DS and the effects of a behavioral intervention in promoting PAP adherence in children with DS and OSAS. The risks to the participant are not greater than minimal, and participants will be carefully monitored to avoid significant risks.

9.5 Recruitment Strategy

CHOP CCHMC and University of Miami potential study participants (children with DS who are diagnosed with OSAS and prescribed PAP) will be identified in a variety of clinical settings: specialty clinics of study partners (for example, Trisomy 21 clinic, pediatric sleep medicine) or from the roster of children scheduled for clinical PSG for suspected SDB in the sleep laboratory. Recruitment via EMR will be used where available.

To facilitate efficient recruitment based on our prior experiences, study staff will review clinic and sleep lab schedules of the DS study partners to identify potential study participants with DS and OSAS. After the clinical encounter, study staff circle back with the study partners to confirm potential eligibility, then reach out to families to gauge interest and further screen those families who are interested in participation, and schedule a screening and consent visit. Study staff will track potential participant willingness to be contacted about study participation.

Caregivers who do not speak English well enough to complete behavioral and performance measures as most are available and validated only in English. In addition, the psychologist in the team speaks English only and would require translation to deliver the intervention to non-English speaking families. This would add a difficult to account for extra-variable based on different languages and different translators.

9.6 Informed Consent and HIPAA Authorization

At both sites, all aspects of the study will be explained in detail to each family by a certified clinical research coordinator who has been trained to work with children with varying developmental abilities. While reviewing all aspects of the study, the coordinator will review a visual storybook of all study-related procedures in which the child will be asked to participate. All questions will be answered and participants and families will be given time to consider their decision. They will be informed of the nature of this research, its potential benefits and possible risks. They will be informed that they are free to refuse participation or to withdraw from the study and that this will not affect any future medical care. The study

team will obtain fully informed, written consent from parent(s) or legal guardians, The families will be given a printed copy of the signed, informed consent.

Participants who may turn 18 during the study: The subject's legally authorized representative will be asked to sign the currently approved version of the consent form at the earliest in-person opportunity.

9.6.1 Waiver of Consent

Not applicable.

9.6.2 Waiver of Assent

Waiver of assent without a waiver of parental permission under 45 CFR 46.408 will be requested for children with DS. Waiver of HIPAA Authorization

A waiver of HIPAA authorization per 45 CFR 164.512(i)(2)(ii) is requested for the review of medical records and recording of PHI for recruitment purposes.

9.7 Payment to Subjects/Families

The following amounts will be paid to the dyad for the inconvenience of participating in the study. Note that all participants will undergo neurobehavioral testing at 0, 6, and 12 months and one titration sleep study at month 3 approximately. Participants randomized to SC will come to 3 research visits and those randomized to INT to 3 research visits. Participants randomized to INT will receive 7 phone calls by the research psychologist and 8 calls from the research coordinator. Participants in the SC will receive 8 phone calls from the research coordinator.

Compensation will vary depending on intervention arm. Subjects not completing the study, for whatever reason, will be paid on a pro rata basis.

9.7.1 Reimbursement for travel, parking and meals

Participant dyad reimbursement will be $75 daytime visits, $100 for sleep study, and $10 for phone calls. Children aged 6-9 years 11 months will not receive money directly but will be given in trust to caregivers. Children ages 10 years and old will receive reimbursement directly.

9.7.1.1 Payments to parent for time and inconvenience (i.e. compensation)

At all sites the SOC arm caregivers will be compensated $50 for each daytime visit (5), $50 for titration sleep study visit, and $10 for each Research Coordinator phone call (8). In total, the SOC caregivers will receive ($380). In the INT arm, caregivers will receive $50 for daytime visits (5), $50 for titration sleep study and $10 for each Research coordinator (8) and Psychologist (7) phone call in which they answer. In total, the INT caregivers will receive ($450).

9.7.1.2 Payments to child participant for time, effort and inconvenience (i.e. compensation)

At all sites child participants in both arms will be compensated $25 for each daytime visit (5) and $50 for the titration sleep study. All child participants will receive a total of ($175).

	Standard Care			Behavioral Intervention		
	Caregiver	**Participant**	**Total**	**Caregiver**	**Participant**	**Total**
Titration PSG	$50	$50	**$100**	$50	$50	**$100**
Assessment Visits (Baseline, 1 Mth, 3 Mth, 6 Mth, 12 Mth)	$50/Visit*5 Visits = $250	$25/Visit*5 Visits =$125	**$375**	$50/Visit*5 Visits=$250	$25/Visit*5 Visits =$125	**$375**
Research Coordinator Calls (8 Calls)	$10/call*8 calls =$80	0	**$80**	$10/call*8 calls=$80	0	**$80**
Psychologist Calls	0	0	**0**	$10/call*7 calls=$70	0	**$70**
Total	$380	$175	**$555**	$450	$175	**$625**

9.7.2 Gifts

Small gifts such as stickers and toys of less than $5 will be given to the children at the visits to keep them engaged. Caregivers and participants will also receive $5.00 meal tickets each for breakfast/lunch during study visits. Participants who also wear their PAP device at any point from ≥80% of nights for ≥6 hours, will also receive a PAP Champion trophy.

10 PUBLICATION

It is anticipated that data from this protocol will be published in a peer-reviewed journal. No individually identifiable PHI will be published.

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