IMPACT OF TREATMENT OF MILD SLEEP-DISORDERED BREATHING ON CHILDREN'S HEALTH

Abbreviated title: Pediatric Adenotonsillectomy for Snoring; PATS

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LIST OF ABBREVIATIONS

ABAS	Adaptive Behavior Assessment
ADHD	Attention deficit hyperactivity disorder
AHI	Apnea hypopnea index
AT	Adenotonsillectomy
BRIEF	Behavior Rating Inventory of Executive Function
BMI	Body mass index
BP	Blood pressure
CBCL	Child Behavior Checklist
CHOP	Children's Hospital of Philadelphia
CCC	Clinical Coordinating Center
CRF	Case report form
DCC	Data Coordinating Center
DMS	Data Management System
DSMB	Data Safety and Monitoring Board
eAT	Early adenotonsillectomy
EEG	Electroencephalogram
ECG	Electrocardiogram
EDC	Electronic data capture
EDF	European data format
EMG	Electromyogram
EMR	Electronic medical record
ENT	Ear Nose Throat
EOG	Electrooculogram
FTP	File transport protocol
GNG	Go-No-Go
HCU	Health care utilization
IRB	Institutional Review Board
ISAAC	International Study Of Asthma And Allergies In Childhood
MOP	Manual of procedures
MSDB	Mild sleep disordered breathing
NHLBI	National Heart Lung Blood Institute
OAI	Obstructive apnea index
OSA	Obstructive sleep apnea
PedsQL	Pediatric Quality of Life Inventory
PSQ	Pediatric Sleep Questionnaire
PSG	Polysomnogram
RCT	Randomized controlled trial
SDB	Sleep-disordered breathing
SES	Socioeconomic status
WWSC	Watchful Waiting with Support Care

STUDY SUMMARY

Title	Impact of Treatment of Mild Sleep Disordered Breathing (MSDB) on Children's Health
Short Title	PATS (Pediatric Adenotonsillectomy for Snoring)
Special Population	Children (male and female), ages 3.0 to 12.9 years of age
Methodology	Parallel, randomized, single blind, multi-center design
Study Duration	5 years
Clinical Study Center(s)	Multicenter (7)
Objectives	1. Determine the effect of early adenotonsillectomy (eAT) on behavior (primary outcome), sleep-disordered breathing (SDB) symptoms, and quality of life. 2. Determine the effect of AT on health care utilization (HCU) in children with MSDB. 3. Identify factors that moderate the response to surgery: age, socioeconomic status, asthma and atopy, second hand tobacco smoke exposure, family functioning, short sleep duration, obesity, minority status
Number of Participants	460
Diagnosis and Main Inclusion Criteria	Diagnosis of mild sleep-disordered breathing (MSDB) defined by an obstructive apnea index (OAI) <1/hr or an apnea hypopnea index (AHI) <or =3.0 /hr confirmed by nocturnal polysomnography (PSG); parental report of habitual snoring (on average occurring > 3 nights per week); tonsillar hypertrophy ≥2 +; deemed to be a surgical candidate for adenotonsillectomy (AT) by ENT evaluation
Study Intervention	Early Adenotonsillectomy (eAT)
Reference Intervention	Watchful Waiting with Supportive Care (WWSC)
Duration of Follow-Up	12 months
Statistical Methodology	Primary analyses will follow the "intention-to-treat" principle; that is, individuals will be analyzed according to their assigned treatment group, whether or not they remain on the study treatment. The co-primary outcomes will be the change in executive behavior relating to self-regulation and organizational skills (as measured by the Behavior Rating Inventory of Executive Function [BRIEF2/P] Global Composite Score) and vigilance (as measured on the Go-No-Go [GNG]) between the eAT and WWSC groups at 12 months. Analyses addressing secondary aims will be considered exploratory. Details of the statistical plan are outlined in the Data Coordinating Center application.

Rationale for the PATS Study

Adenotonsillectomies are performed more than 500,000 times per year in the US[1], and are the 2nd most common surgery performed under general anesthesia in children[2]. The majority of surgeries are performed for obstructed breathing rather than for infection or other indications[2]. We recently addressed the role of adenotonsillectomy (AT) in improving the 7-month neurocognitive, behavioral and health outcomes of children with frank obstructive sleep apnea (OSA). The results of this rigorous, multicenter, randomized controlled trial (Childhood Adenotonsillectomy Trial; [CHAT]) were published in the *New England Journal of Medicine*[3] and provided critically important data indicating that AT compared to watchful waiting resulted in improved behavior, quality of life, sleep-disordered breathing (SDB) symptoms and polysomnographic parameters. However, this study addressed the role of surgery in the minority of operative candidates who have frank OSA, only one form of SDB on a spectrum that includes a more common phenotype, namely primary snoring (also termed mild SDB [MSDB])[4]. MSDB is characterized by snoring without frank obstruction or gas exchange abnormalities and has a population prevalence of about 10% in children[5]. Since most surgeries for obstructed breathing are performed for MSDB rather than OSA[6], the next logical question is whether surgery is also effective in improving symptoms and health outcomes in this large group of children.

We propose to take advantage of a successful collaboration of leaders in sleep medicine, otolaryngology and clinical trials to efficiently leverage experiences from CHAT to evaluate the role of AT in children with MSDB. We aim to resolve uncertainties on management approaches for pediatric MSDB by addressing several critical issues: a) assess outcomes of importance to children and their families - in particular, the patient-reported outcomes of behavior, quality of life, and sleep disturbances; b) examine differences in treatment responses among children who are at increased risk for MSDB, such as pre-school children, minorities, and children with asthma or obesity; c) evaluate health care utilization (HCU) as a unique and timely outcome; d) assess moderating influences of second hand smoke, insufficient sleep, socioeconomic status (SES) and family functioning; e) examine longer term outcomes than were feasible in the CHAT study (12 months).

These aims have substantial public health significance given the high morbidity of SDB in children[7] and the vulnerability of certain groups such as African Americans, who have a higher prevalence[8] and increased severity of SDB compared to children of other races[3]. Large health care costs arise from AT, which is also associated with surgical morbidity, including significant hemorrhage in 3% of patients, and death in 1 in 16 000 to 35 000[2]. Although the cumulative cost of AT is high, these costs must be balanced by the costs of untreated MSDB. Research from Israel suggests that children with OSA have increased HCU in the year prior to their diagnosis[9], which declines by one third following AT[10]. Given the rising health care costs in the US[11], there is a critical need to address this question in the US and to evaluate children with MSDB who constitute the majority of children with SDB. Finally, tremendous practice and geographic variability exists in the management of SDB due to the paucity of clear guidelines. For example, while the American Academy of Pediatrics and the American Academy of Sleep Medicine recommend polysomnography (PSG) prior to AT, with subsequent surgery only if PSG shows OSA[12;13], other medical societies do not support this view[2;14]. **Indeed. the American Academy of Otolaryngology—Head and Neck Surgery Clinical Practice Guideline on Polysomnography for Sleep-Disordered Breathing Prior to**

Tonsillectomy in Children recommends PSG in children with suspected sleep-disordered breathing only if the child has complex medical conditions such as Down syndrome, or if the need for surgery is uncertain and there is a discrepancy between symptoms and clinical exam[14]. In fact, PSG is performed prior to AT in only 10% of children undergoing surgery for suspected OSA.[6] Less than 50% of children scheduled for AT for suspected OSA actually have abnormal PSGs; the remainder have MSDB[3;7]. This study will provide evidence on whether children with "normal" PSGs benefit from surgery, by randomizing children to the two most common managements for MSDB: adenotonsillectomy and observation. The findings will have key implications for disease management, including the need for pre-operative PSGs to establish the diagnosis of OSA.

Significance

Mild sleep-disordered breathing (MSDB; snoring without frank obstruction or gas exchange abnormalities on polysomnography[15]) is an extremely common disorder. Large studies of more than 1,000 children each have shown an MSDB prevalence of 10.5-17.1% in young children in the USA[5;16;17], and MSDB is one of the commonest indications for adenotonsillectomy (AT). Given the high prevalence of the condition, the relevance of the study's outcomes to patients and the health care system, the large geographical variations in care resulting from lack of data on the role of surgery and polysomnography (PSG) in this population, and the vulnerability of a young population (often minority) with the disorder, MSDB is of great clinical and public health relevance. The proposed study will address gaps in the literature by: a) enrolling very young children who are at greatest risk for MSDB and its potential neurobehavioral consequences; b) following children for a full year after intervention to obtain reliable estimates of changes in health care utilization and behavior that are not biased by seasonal effects[18]; c) analyzing the influence of both individual and family-level factors in modifying responses to treatment; d) enrolling children with MSDB, who are the largest group who undergo AT, an expensive procedure with significant morbidity. The proposed study (Pediatric Adenotonsillectomy Trial for Snoring; PATS) will provide data from a randomized controlled trial that for the first time will address the role of AT in children with MSDB, and define the subgroups most suitable for this procedure.

Importance and Public Health Significance: Tonsillectomies are performed more than 500,000 times per year in the US and are the second most common surgery under general anesthesia in children, resulting in $400 million annual costs. Adenotonsillectomy is most commonly performed for the treatment of pediatric obstructive sleep apnea or MSDB, often with the expectation that surgery will improve behavior, quality of life and cognition. The recently completed CHAT study demonstrated that surgery resulted in improved patient and family centered outcomes - behavior and quality of life - in children ages 5-9 years with polysomnographic evidence of OSA, although cognitive ability did not change[3]. This new information will assist with clinical decision making for children with OSA. However, data are not available on the benefits of surgery for treatment of MSDB, or for treating younger children, who may be most sensitive to the effects of sleep problems due to developmental plasticity. There is a pressing need to address this question since young children with MSDB constitute the majority of children referred for AT[19]. Lack of data has led to huge geographical variability in the management of this disorder, with the rate of AT per 10,000 children varying from 28.9 in the West to 125.1 in the South of the USA[19]. Inappropriate surgery may unnecessarily expose children to risk, and the health care system to considerable

costs. Conversely, withholding effective treatment from children likely to respond could result in substantial short and long-term health burdens to the child, their family, and society. This information is also needed due to the increased prevalence of SDB among vulnerable groups of children, such as racial minorities. Filling these gaps in knowledge is critical for informing clinical guidelines and decision-making, and appropriate utilization of interventions in populations most likely to benefit.

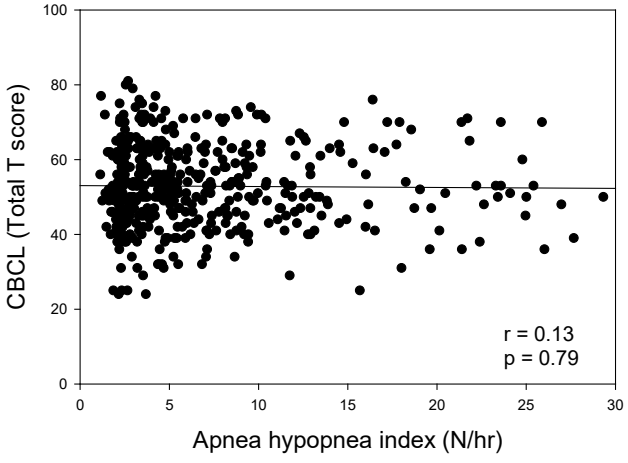
MSDB: Prevalence and Health Impact: Most tonsillectomies are performed for obstructed breathing (determined clinically by history and examination) rather than for infection or other indications. The vast majority of children undergoing AT for obstructed breathing do not undergo PSG: only 4% of pediatric otolaryngologists obtain polysomnograms "most of the time" to diagnose OSA prior to AT[20]. Patients at major academic medical centers may be more likely to undergo polysomnography before AT, in part because more complex patients are evaluated at these centers (e.g., infants or patients with major comorbidities, unlike those eligible for the current study). However, even at academic centers, the majority of children undergoing AT for SDB do not have polysomnography. For example, 977 children underwent AT at Children's Hospital of Philadelphia between May 2012 to March 2013, of whom only 386 (39%) had a polysomnogram in the preceding 12 months. Thus, 61% did not have polysomnographically proven OSA. Although some of these surgeries may have been performed for infectious or other non-obstructive reasons such as tumor, the number far exceeds the percentage of AT performed at Children's Hospital of Philadelphia for non-obstructive reasons (~20%; personal communication from Lisa Elden, MD). Thus, the majority of children undergoing AT for symptoms of SDB do not have polysomnography.

Of children with clinically suspected SDB, numerous studies have shown that when PSG is performed, approximately 50% do not have frank airway occlusion or gas exchange abnormalities[3;7], but have MSDB and are classified as "primary snorers." Thus, AT for MSDB is usual care. Snoring is due to vibration of upper airway tissues during sleep, secondary to upper airway narrowing and sleep-induced pharyngeal hypotonia, and results from increased upper airway resistance. The consequent airflow limitation may cause a variety of physiological responses, including sleep fragmentation, autonomic nervous system dysfunction, vagal neuroreceptor activation and gastroesophageal reflux. Of note, snoring itself, in the absence of apnea, has been linked to hypertension[21] and asthma exacerbations[22;23] in adults, and to hypertension[24], behavioral disturbances[25] and poor asthma control[26] in children. Evidence exists that snoring is a mechanical stress and may cause upper airway neuronal damage and myopathy secondary to vibrational damage (similar to hand-arm vibration syndrome caused by vibrating hand-held tools)[27-29], neutrophilic airway inflammation (characteristic of severe and difficult to treat asthma)[30;31], and direct damage to carotid vessels[32].

Both OSA and MSDB have been shown to be associated with behavioral dysfunction in children (including attentional issues, hyperactivity, social withdrawal and anxiety), which has a significant potential to impair learning, academic performance, and quality of life, and thus to negatively impact childhood health and well-being as well as curtail future adult potential. The CHAT study is the only large, randomized controlled trial of neurobehavioral outcomes in children with SDB[3]. This study was limited to children with

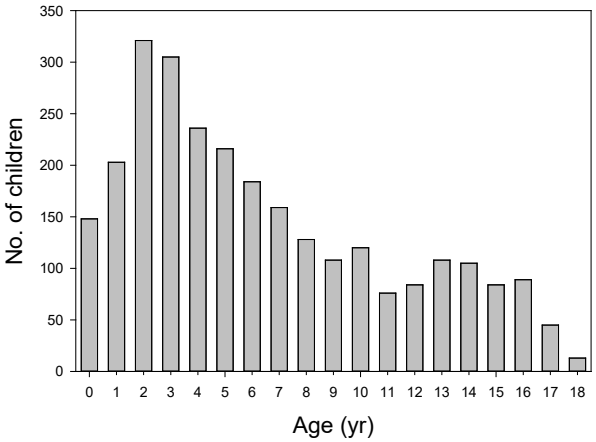
polysomnographically-proven OSA. We showed that children with OSA had significant improvements in the important areas of behavior, quality of life, SDB symptoms and polysomnographic parameters following AT compared to children randomized to watchful waiting with supportive care (WWSC), although no improvements were seen in cognition over a 7 month observation period[3]. However, this study showed no correlation between the severity of polysomnographic abnormalities and behavioral deficits, or with the behavioral response to intervention. For example, although there was a significant improvement in the Child Behavior Checklist (CBCL) measure of behavior in the eAT group compared to the WWSC group (change over 6 months of -3.8 + 8.1 *vs* -1.2 $\pm$ 7.9, p<0.001), the baseline CBCL did not correlate with the baseline apnea hypopnea index (AHI; Figure 1) or other measures of PSG severity. Similarly, studies in adults have failed to show a relationship between polysomnographic severity and daytime outcomes[33]. Small, nonrandomized observational studies have shown impaired attention, social problems, anxiety and depressive symptoms in children with MSDB without OSA, as compared to controls[34;35]. The importance of behavioral outcomes in children with MSDB is also supported by preliminary research by members of our team. Chervin studied 40 children with OSA, 38 children with MSDB and 26 controls[25]. Children with both OSA and MSDB had worse behavior and hyperactivity compared to controls, and in both groups, behavior improved 12 months after AT. A comparison of the OSA and MSDB groups showed that they had similar behavioral scores at baseline, and also both showed similar levels of behavioral improvements after AT, suggesting that MSDB may have as important an effect on behavioral disturbances as OSA. Marcus studied 108 children presenting with symptoms of SDB and 72 controls[36]. Although patients with SDB had increased sleepiness (modified Epworth Sleepiness Scale 8.1$\pm$4.9 *vs* 5.3$\pm$3.9, p<0.001) and symptoms of attention deficit-hyperactivity disorder (ADHD)(Conners Abbreviated Symptom Questionnaire 12.8$\pm$7.6 vs. 9.0$\pm$6.2, p<0.001) compared to controls, there was no difference in sleepiness or ADHD symptoms in patients with MSDB *vs* OSA. In the Cleveland Children's Sleep and Health study, investigators Rosen and Redline evaluated 835 children from a community cohort which include a wide range of SDB[37]. After adjusting for confounding variables, cognitive deficits were associated with parent-reported habitual snoring (i.e., MSDB), but not with polysomnographic parameters such as arterial oxygen saturation levels or the AHI. Thus, these studies indicate that children with MSDB have poorer neurobehavioral outcomes than controls and suggest that these outcomes may be reversible with AT. However, these studies had limitations and confounding factors inherent to their nonrandomized design; thus the current proposed randomized controlled trial is required for a definitive assessment of the potential benefits of AT on behavior in this large group of children with MSDB for whom there is a lack of research to inform clinical decision making.

Figure 1: Correlation between CBCL and AHI



Health Care Utilization (HCU):
Escalating health care costs highlight the need to use evidence such as data on the value of treatment to both patients and the health care system when making treatment decisions. Both untreated childhood SDB and its treatment, AT, are associated with large health care costs.

Fig. 2: Age distribution of patients with SDB



A European study estimated the total societal costs of an uncomplicated tonsillectomy to be 1,074 Euros[41]. Thus, the economic impact of tonsillectomy is enormous considering the number of surgeries performed each year. There is also significant morbidity associated with AT, including post-operative hemorrhage (~3% of patients), respiratory compromise and post-operative pulmonary edema, dehydration, nasopharyngeal stenosis, velopharyngeal incompetence[2] and death[42]. Although the cumulative cost of AT is high, these costs must be balanced by the economic and health costs of untreated SDB. Research from Israel has shown that children with OSA have health system utilization that is 225% higher than controls in the year prior to their diagnosis, indicating that these children are a financial burden on the health care system. Notably, these uncontrolled data indicate that health care costs decline by one third following AT[10;43]. Decreased costs were largest in the youngest children (whom we intend to study), and were attributable to changes in number of hospitalizations, emergency department visits, consultations (ENT, pulmonary and allergy) and medication use (primarily asthma, allergy and antimicrobial drugs). The Israeli studies were limited by the modest sample (with little power to detect differences due to obesity, asthma and other risk factors) and no data on other relevant risk factors and outcomes, such as behavior and quality of life, which may importantly modify by treatment response and complement data on HCU. Although the Israeli data suggest that HCU is lower in children with milder SDB, their sample did not include African Americans and may not represent HCU patterns in the US. Given that the majority of children undergoing AT in the US have MSDB, there is an urgent need to assess HCU in this population. Thus, a randomized controlled trial is required to determine whether the benefits from this frequently performed surgery outweigh the risks, as well as to better inform rational use of limited health care resources. Changes in HCU will be evaluated in Aim 2.

Effect of Age on Behavioral Response to AT: SDB has been shown to affect neurobehavioral and cognitive function across the age span. However, only a handful of studies have evaluated young (preschool) children despite the fact that SDB is more common in preschool-aged children than older children. Figure 2 shows the age distribution for the 2,732 children who underwent PSG at Children's Hospital of Philadelphia in 2012; 757 (28%) were aged 3-5 years, and 579 (21%) were aged 6-9 years. Preschool children are likely the most at risk for neurocognitive impairment, due to the rapidly developing nervous system at that age, and the importance of sleep in preserving memory and learning[44], although they may also be the most likely to show improvement if treated early, due to central nervous system plasticity. By recruiting children as young as 3 years of age, we will fill an important knowledge gap in research in young children. In Aim 3 of this proposal, we will examine the modifying effect of age on the response to surgery in children with MSDB.

Racial Health Disparities, Socioeconomic Status (SES) and SDB: We[8;45;46] and others[47-49] have shown that African American adults and children have a higher prevalence of SDB than Whites, even when controlled for factors such as obesity and

SES; the prevalence of SDB in African American children is 3.5 to 6.0 fold higher than that of Whites. The CHAT study showed that African American children with OSA had smaller relative improvements in behavior following AT compared to children of other races, even when controlling for obesity, baseline behavioral scores and parental income (Table 1). Although African American children have a higher prevalence of SDB and more sequelae thereof, they are less likely to undergo AT[50;51], with one study showing a threefold prevalence of AT in White compared to African American children[50]. Further, PI Marcus prospectively followed 329 high risk children undergoing AT for SDB, and found that African American race was a predictor of post-operative respiratory complications (35% of African Americans *vs* 24% of children of other races, p=0.036)[52]. Thus, African American children have a higher prevalence of SDB but are less likely to undergo AT, and if they do, they have an increased rate of complications and less behavioral improvement. The reasons for these racial differences are unclear but may include differences in craniofacial anatomy, adipose tissue distribution, ventilatory drive and inflammatory responses. Racial differences in sleep quantity have also been found, with African American children reporting less nocturnal sleep, increased daytime napping and overall less sleep than children of other races[53-55]. This is important, as even one hour less of sleep per night can affect neurocognitive and behavioral functioning[56]. In addition, we have shown that SDB is associated with lower SES, independent of race and obesity[57], a finding that may be partially explained by exposures to second hand smoke, environmental irritants and allergens. Low SES parents also may have decreased medical literacy, which may impede their management of SDB-related co-morbidities (such as asthma) or influence sleep practices.

Further data are needed to understand the response to surgery in African American children and in lower SES families, in order to optimize their management and reduce health disparities. This will be evaluated in this study through a comprehensive consideration of factors that may modify treatment responses, including obesity, sleep duration, asthma/atopy and family functioning.

Table 1: Relative improvements in behavioral measures between races

	African American		**Other races**		
	eAT	WWSC	eAT	WWSC	P value
Conners	-1.06 ± 10.85	-0.98 ± 9.53	-4.84 ± 9.49	0.61 ± 9.22	*p<0.01
BRIEF	-1.82 ± 8.86	-0.30 ± 9.27	-4.98 ± 7.69	1.17 ± 8.29	*p<0.05
PSQ-SRBD	-0.24 ± 0.19	-0.04 ± 0.19	-0.32 ± 0.16	-0.02 ± 0.18	*p<0.01

*P value for interaction between race and treatment

Asthma*:* Asthma accounts for nearly $60 billion of total costs per year in the US[58] and is the leading cause of hospitalizations and school absenteeism in children. Asthma and SDB frequently co-aggregate, with evidence of bi-directional links between these two common conditions[59]. Children with habitual snoring have an increased risk of asthma compared to non-snorers (odds ratio 1.48 to 3.27)[60-64]. Investigators Redline and Ross demonstrated that children with asthma had a 27 - 43% prevalence of habitual snoring[26;59], substantially higher than the 10% seen in the general pediatric population[7]. Further, they and others have shown that SDB is associated with severe or difficult to treat childhood asthma, independent of BMI and race[26;65]. There are several biologically plausible mechanisms by which SDB could adversely influence asthma, including

mechanical, inflammatory, metabolic, and autonomic nervous system effects. Notably, the increased work of breathing associated with SDB can induce neutrophilic airway inflammation, which is a characteristic of severe and refractory asthma[30;31]. We have shown that children with asthma and untreated SDB had a 3.7-fold greater one year rate of asthma exacerbations, as measured by medication use, symptoms and HCU, compared to children without SDB[26]. An uncontrolled study indicated that asthma control may be improved by AT. In this study of only 35 children, asthma exacerbations decreased from 4.1 ± 1.3 per year to 1.8 ± 1.4 per year after AT[65]. Although untreated MSDB may exacerbate asthma, no prior research has addressed the role of AT in influencing asthma-related HCU in children with SDB and asthma. Since asthma is one of the leading causes of HCU in children, it is critical to assess whether AT in asthmatic children with SDB is beneficial. Demonstrating improved HCU among asthmatic children with MSDB treated with AT would change asthma management paradigms. In CHAT, 143 (30.8%) of subjects had asthma, 107 (23%) had hay fever, and 123 (26.5%) had eczema. This is much higher than the reported US prevalence of childhood asthma (10%), hay fever (7-10%) and eczema (12%)[66].

Secondhand Smoke: Multiple studies have shown that secondhand smoke is associated with snoring in children[67;68]. CHAT demonstrated that, among children referred for AT, the AHI was 20% higher in those exposed to second hand smoke than non-exposed children[69]. The proposed objective assessment of urinary cotinine levels will provide a unique opportunity to assess whether secondhand smoke modifies the response to AT. This information may help inform policies that target secondhand smoke during pre-operative planning of AT.

1. Study Objectives

1.1. Primary Objectives

The primary co-objectives are to determine the effect of eAT versus WWSC on executive function (Behavior Rating Inventory of Executive Function [BRIEF2/P] Global Composite Score), and vigilance (Go-No-Go; GNG).

1.2. Secondary Objectives

To determine the effect of eAT versus WWSC on sleep-disordered breathing (SDB) symptoms, and quality of life health care utilization (HCU). We will track and compare group changes in health care utilization: sick days/intercurrent illness, asthma exacerbations; prescriptions and over-the-counter medication use; ambulatory or hospital encounters. Exploratory outcomes include change in anthropometry and blood pressure.

To identify factors that moderate the response to surgery including age, socioeconomic status (SES), race, asthma/atopy, secondhand smoke exposure, short sleep duration and assessment of family function competency.

As an exploratory aim, to determine whether quantitative snoring metrics from the Tascon DR-10L Snoring Microphone correlate with the above outcomes.

As an exploratory aim, to determine whether participants would be willing to be contacted with long-term follow-up questions to assess the feasibility of conducting a study to evaluate the long-term outcomes in children with mild sleep disordered breathing, and to exam the number of children that sought additional treatment for sleep disordered breathing after their one-year participation period.

2. Study Design

2.1. General Design

This will be a randomized, single-blind 12-month intervention study that compares the impact of AT on measures of behavior, quality of life and HCU in children with MSDB. The proposed study will involve participation of children and their caregivers. Children with symptoms of MSDB will be recruited from each site's sleep clinics and laboratories, otolaryngology clinics, asthma clinics and general pediatric clinics. Potentially eligible children who are reported to be snorers at each site will be identified through systematic screening of health records and parent interviews. Children who meet study eligibility criteria will be randomized to having either eAT or WWSC for 12 months. In addition to the enrollment PSG at baseline, participants will receive behavioral testing, assessment of SDB symptoms, sleepiness, quality of life, anthropometry, and blood pressure. PSG and baseline measures will be repeated at 12-months. At 6 months caregivers will complete neurobehavioral assessments remotely, except for Virginia , where they will have an in person visit with child neuro behavior testing. Potential factors that may affect response to AT will also be assessed (asthma and atopy, secondhand smoke exposure, , family functioning). Approximately 920 participants will undergo baseline screening PSG, and 460 participants will be randomized. Both genders and all racial and ethnic groups will be eligible for participation. Participants failing baseline screening PSG will be referred for clinical care. It is anticipated that ~50% of participants will be eligible after PSG.460 eligible children, 230 per treatment arm, will be randomized to one of two treatment groups, and followed for a 12-month period.

Eligible participants will be randomized to one of two management groups:

1. Early Adenotonsillectomy (eAT) performed by participating ENT surgeons within 1-4 weeks of randomization.

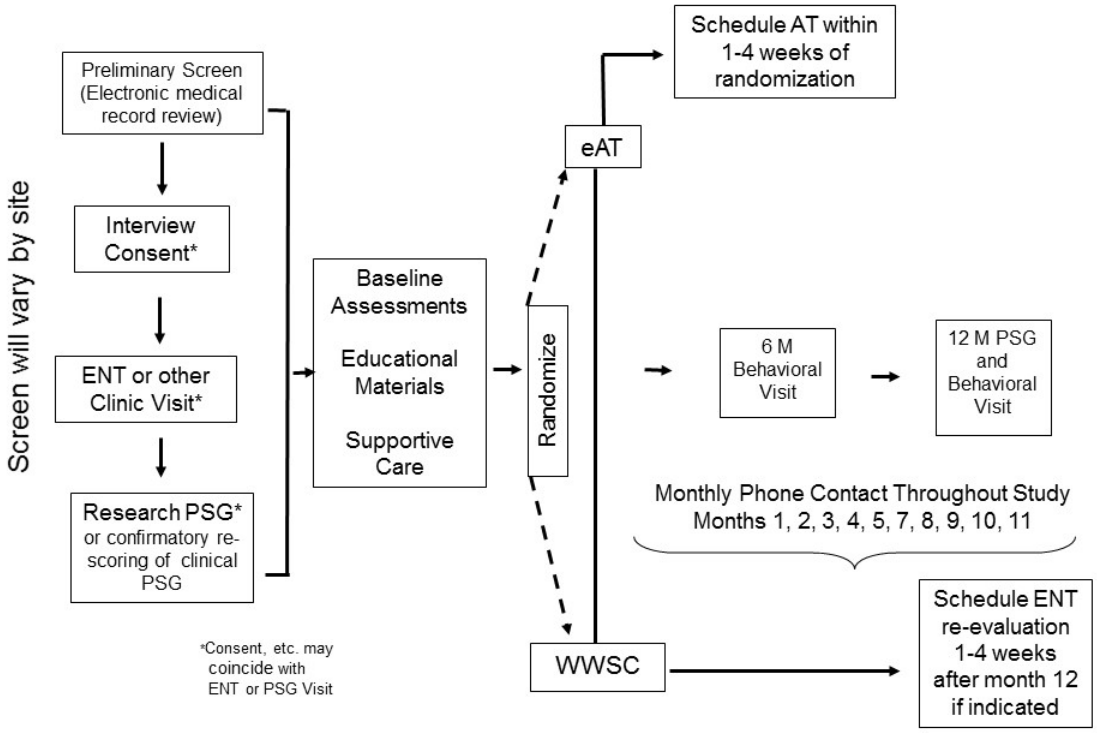
2. Watchful waiting with Supportive Care (WWSC)

Participants in both groups will receive verbal and written information about healthy sleep habits guidance. Participants will be referred for appropriate "usual care" for relevant co-morbidities (for example, poorly controlled asthma, allergies) identified by the study team as needing further optimization of management.

Participants will undergo a standardized assessment of behavior, behavioral performance testing, and other health-related evaluations at baseline and 12 month follow-up time points. At 6 months caregivers will complete neurobehavioral assessments remotely. Virginia will have a 6 month visit in person and repeat baseline assessments. Participants will receive monthly check-in by telephone, , email and/or text messaging in order to maximize retention and to collect additional symptom and HCU reports. Text messaging will only be utilized with families who agree to receive text messages. After 12 months, children who did not get surgery who have a 12-month

PSG showing obstructive sleep apnea (apnea hypopnea index ≥3 /hr or obstructive index > 1/hr) or whose parent reports ongoing symptoms/concerns will be referred back to ENT for further clinical management (such as adenotonsillectomy) as per standard clinical care.

2.2. Study Schema



6-month visit, remote collection of parent behavior assessments at all sites except Virginia

2.3. Blinding and Maintaining the Blind

The study will be single blinded since sham surgery, including use of general anesthesia, would not be ethical, and evidence of tonsillectomy is evident. All members of the Clinical Coordinating Center, research personnel and Steering Committee members, including investigators, quality control personnel, scorers, data entry staff, polysomnologists, and staff performing anthropometry, behavioral testing, and blood pressure, will be blinded to the study arm. Unblinded personnel include the research coordinator who will make the intervention appointments, the otolaryngologist performing the surgery, the research coordinator making monthly contact by telephone, email, and/or text messaging and assessing for adverse events, the study's external Medical Safety Monitor, and selected DCC personnel. The unblinded research coordinator will not be administering any tests or measurements that could be influenced by interview or administration technique. If cases of unblinding are identified, a protocol deviation will be reported.

Each site will designate an unblinded research coordinator/assistant who will have knowledge of the treatment arm assignment. The unblinded research coordinator will be responsible for informing the parent/legal guardian of the treatment arm assignment, making follow-up contact by telephone, , email and/or text messaging, assessing for AE's, scheduling AT within 1-4 weeks for the eAT group, and scheduling WWSC re-evaluation after the Month 12 visit.

2.4. Overview of Study Design

See Appendix A for a summary of study visits and all study related procedures

2.4.1. Screening Visit

Screening of ENT, sleep clinic, general pediatric or other internal clinical practice patients (including electronic medical records [EMR] and existing PSG review) will be performed to identify potentially eligible participants to ascertain preliminary study eligibility. Outside referring physicians will be contacted for permission to approach external practice patients. All HIPAA requirements will be met.

- Obtain informed consent and confirm further eligibility criteria with parent interview (at face-to-face encounter).
- Refer for ENT evaluation (if not done within 3 months of randomization) to confirm surgical candidacy.
- Arrange a research baseline PSG with central scoring. (If a standardized clinical PSG is available, this will be obtained and centrally scored to confirm final eligibility criteria.)
- Perform the ABAS-III if possible (if time does not permit, this will be performed at the baseline visit).

2.4.2. Baseline Visit

- Perform baseline assessments and procedures: behavioral and performance testing and questionnaires including the parent-completed BRIEF2/P; weight, height, anthropometry, and blood pressure measures; lab tests (serum IgE, urinary cotinine); provide healthy sleep guidance; ; mail teacher behavioral rating scales. To ensure that at least one of the primary co-outcomes is available, the parent version of the BRIEF2/P must be completed before a participant can be randomized.
- Randomize to eAT *versus* WWSC

2.4.3. Follow-up Contacts

eAT arm only*:* AT surgery 1-4 weeks from randomization within Month 1

WWSC arm only: ENT re-evaluation visit with 1-4 weeks after Endpoint Visit if indicated by 12-month PSG revealing obstructive sleep apnea (AHI $\geq$3.0 /hr. or obstructive apnea index > 1/hr.) or parent reporting concerning symptoms.

Both groups:

- Monthly contact by telephone, email and/or text messaging , for health care utilization, medication, adverse event inquiries and to support study participation.
- Check In questionnaires and surveys will be completed bi-monthly, at months 2, 4, 6, 8, and 10.
- Interim remote visit at 6 months for caregiver questionnaires and neuro behavioral assessments, adverse event and health care utilization inquiry, and teacher forms of behavior rating scales.
    - Virginia will have in person child neurobehavior testing in addition to assessments above.
- Endpoint Visit at Month 12 for behavioral and performance testing; questionnaires; anthropometry, and BP measures. Behavioral rating scales mailed to teachers.
- Follow-up research PSG at Month 12
- Follow up questionnaires after participation ended to assess feasibility of conducting a study to evaluate long-term outcomes of mild SDB

2.5. Study Organization

The PATS Study Organization consists of the following 7 clinical sites that will recruit participants for this randomized study:

1) Children's Hospital of Philadelphia, Philadelphia, PA
2) Rainbow Babies and Children's Hospital, Case Medical Center, Cleveland, OH
3) Cincinnati Children's Hospital Medical Center, Cincinnati, OH
4) University of Michigan, Ann Arbor Hospital, Ann Arbor, MI
5) UT Southwestern Medical Center, Dallas, TX
6) Boston Children's Hospital, Boston, MA
7) East Virginia Medical Center, Norfolk, VA

Study investigators will interact at annual Steering Committee meetings (in addition to an initial centralized training session) and during monthly conference calls.

In addition to the clinical sites, the organization includes:

- Clinical Coordinating Center (CCC) will be based at Children's Hospital of Pennsylvania and led by Drs. Susan Furth and Lisa Young. The CCC will be responsible for coordinating the clinical activities of each of the clinical sites. The CCC will also provide central analysis of blood and urine samples.
- Data Coordinating Center (DCC) and Sleep Reading Center will be co-directed by Drs. Redline and Rui Wang and will be located at Brigham and Women's Hospital. The DCC will be responsible for generating all case report forms, developing and maintaining the database and study web portal, data audits, conducting the statistical analyses, preparing DSMB reports, and supporting the study communications and quality control. The Sleep Reading Center will provide central scoring of PSGs, confirm PSG eligibility, and provide standardized PSG training and monitoring.

- Additional analyses will be completed by Dr. Wang and staff from Harvard Pilgrim Health Care (HPHC) through a cede review to BWH IRB. To meet the goal of completing analyses for multiple manuscripts using data collected under the auspices of the Data Coordinating Center at BWH, Dr. Wang's group at HPHC will be provided fully de-identified research data collected for this multi-center trial. Dr. Wang and her colleagues at HPHC will access this de-identified dataset through use of a secure FTP transfer. This activity (and data access) will be addressed in an updated subcontract from BWH to HPHC.
- External Medical Safety Monitor (Dr. Heidi Connolly, University of Rochester) will provide safety monitoring and central adjudication of treatment failures and serious and unexpected adverse events. Although all sites are responsible for local reporting of AEs, the Independent Medical Monitor will be responsible for adjudicating the status of potential Treatment Failures as used as a study outcome.
- The NHLBI has established an external DSMB according to NHLBI policies. Members include experts in sleep medicine, biostatistics, pediatrics, neurocognition, surgery, and ethics (some overlapping). The DSMB has convened to review the final protocol and DSMB Charter before study initiation and will continue to meet periodically, and not less frequently than annually. The DSMB Chair and the Independent Medical Monitor will receive all reports of serious adverse and unexpected adverse events and treatment failures in real time. The DSMB has requested to receive interim reports on a quarterly basis sent electronically to all DSMB members. The DCC Project Manager is responsible for assembling materials/reports for the DSMB and NIH and maintaining all regulatory files across the duration of the study.
- The study will be governed by a Steering Committee composed of each PI, and leaders of the Quality Control subcommittees.
- Steering Committee subcommittees will be charged with tasks associated with specific operations and quality control activities and will include Protocol Development, Protocol Operations, Surgical Quality Control, Neurobehavioral Quality Control, Recruitment & Retention, and Publications & Presentations. An external Data Safety and Monitoring Board will be established by NHLBI.

3. Study Endpoints

3.1. Primary Endpoint

The primary co-endpoints are the BRIEF2/P Global Composite Score and the GNG signal detection parameter (*d')*.

3.2. Secondary Endpoints

Secondary measures include data from the following domains:

- Objective performance testing
    - Vigilance/attentional skills: Go-No-Go test subtests
    - Fine motor coordination: NIH-Toolbox 9-Hole Pegboard Dexterity Test

- Behavioral scales (note that several measures utilize a date stamp when questionnaires are entered electronically into the commercial scoring websites)

  - Executive function: BRIEF2/P meta-cognition and emotional regulation summary scores and subscales for parent and teacher reports; BRIEF2/P teacher report global composite score and subscores
  - Behavior: Child Behavior Checklist (CBCL) summary scale and subscores, parent and teacher responses
  - Attention: Conners 3 Short Form (caregiver and teacher versions) Global Index T score and subscales
  - Adaptive Behavior Measure System, 3rd Edition (ABAS-III), a measure of children's everyday functioning (this measure is centrally scored, and date of birth as well as date of study and study ID is required to be entered into the WPSpublish website)

- SDB symptoms
  - Pediatric Sleep Disordered Breathing Questionnaire (SRBD) total score
  - Sleepiness: Epworth Sleepiness Scale modified for children summary score and SRBD sleepiness scale
  - Snoring: The Tascam DLR-10L Microphone results as an exploratory aim

- Quality of Life
  - Generic: Pediatric Quality of Life Inventory (PedsQL) total score and subscores
  - Disease specific: OSAS-18 total score

- Physical exam
  - Measurements of weight; height; body mass index (BMI); waist, hip, neck circumferences
  - Systolic, diastolic, and mean blood pressure levels

- Health Care Utilization
  - Medications, health care visits (scheduled, unscheduled), ascertained from caregiver reports, EMR surveillance, billing and pharmacy records, hospitalizations.

3.3. Sample Descriptors and Potential Effect Modifiers

- Demographics: race, SES (parent education, family income, financial stress rating scale, geocode data on neighborhood characteristics)

- Asthma/atopy: IgE, International Study Of Asthma And Allergies In Childhood (ISAAC) questionnaire, review of EMR and parent interview (using NHLBI asthma definitions based on a history of asthma and use of asthma medications)

- Second-hand smoke exposure: urinary cotinine

- Family functioning cluster: family functioning (Family Assessment Device, short form); parenting style (Parenting Style Questionnaire); parent perception of stress (Parenting Stress Index 4th Ed., short form); medical literacy (Rapid

Estimate of Adult Literacy in Medicine, Revised); discrimination (Experiences of Discrimination)

- COVID-19 Survey

4. Participant Criteria

4.1. Study Population

This study will involve participation of children with symptoms of MSDB and their caregivers. Both genders and all racial and ethnic groups will be eligible for participation. Dyads (child and one caregiver) will be included. The following inclusion and exclusion criteria refer to the child participant only. There are no specific inclusion/exclusion criteria for the caregiver participant. The caregiver participant will be the parent/guardian providing informed consent or accompanying the child on the study visits.

4.2. Inclusion Criteria

1. Ages 3.0 to 12.9 years at the time of screening

2. Diagnosed with MSDB defined as:

    a. Parent report of habitual snoring that occurs most of the night on at least 3 nights per week, and has been present for at least 3 months (on average occurring > 3 nights per week or more than one-half the sleep time) *and*
    b. Obstructive apnea index < 1/hr or obstructive apnea hypopnea index <3 /hr and no desaturation < 90% in conjunction with obstructive events, confirmed on nocturnal, laboratory-based PSG

    NOTE: Participants failing baseline screening PSG will be referred for clinical care.

3. Tonsillar hypertrophy ≥ 2 based on a standardized scale of 0-5
    a. 0 = surgically absent
    b. 1 = taking up < 25% of the space between the tonsillar pillars
    c. 2 = taking up 25-50% of the space between the tonsillar pillars
    d. 3 = taking up 51-75% of the space between the tonsillar pillars
    e. 4 = taking up > 75% of the space between the tonsillar pillars

4. Deemed to be a candidate for AT by ENT evaluation, i.e., no technical issues that would be a contraindication for surgery such as submucous cleft palate.

5. Primary indication for AT is nocturnal obstructive symptoms (i.e., not recurrent infections or other indications)

4.3. Exclusion Criteria

1. Previous tonsillectomy (whether partial, i.e., tonsillotomy, or complete tonsillectomy).

2. Recurrent tonsillitis that merits prompt AT per the American Academy of Otolaryngology-Head and Neck Surgery Clinical Practice Guidelines, i.e., ≥ 7

episodes/yr. in the past year; ≥ 5 episodes/year over the past 2 years or ≥ 3 episodes/yr. over the past 3 years[2].

3. Severe obesity (BMI z-score ≥ 3)

4. Severe chronic health conditions that might hamper participation or confound key variables under study. These conditions include, but are not limited to:

   - severe cardiopulmonary disorders (e.g. cystic fibrosis, congenital heart disease)
   - bleeding disorders
   - sickle cell disease
   - epilepsy requiring medication
   - other severe chronic health problems such as diabetes or narcolepsy.
   - mental retardation or assigned to a self-contained classroom for all academic subjects
   - known genetic, craniofacial, neurological, or psychiatric conditions likely to affect the airway, cognition, or behavior
   - psychiatric or behavioral disorders requiring or likely to require initiation of new medication, therapy, or other specific treatment during the 12-month trial period (other than ADHD).

5. Current use of psychotropic medication (other than medications for ADHD), hypnotics, antihypertensives or growth hormone. Note that children with ADHD will be included as it is possible that some cases of ADHD are secondary to MSDB

6. History of severe developmental disability or ABAS score < 60

7. Parent/guardian unable to accompany the child on the night of the PSG

8. Family planning to move out of the area within the year

9. Family does not speak English or Spanish well enough to complete the behavioral and performance measures.

10. Children in foster care.

4.4. Deferral Criteria

There may be some situations or conditions for which a participant will be deferred from entry into the study. Once it is formally ascertained that the condition is not present or has subsided according to the time frame identified, the participant will be reconsidered for entry into the study. The following list identifies some of the conditions for deferral:

1. Participants currently enrolled in another intervention or longitudinal study.

2. Participants who have received an investigational drug or device within 30 days prior to screening will be deferred until off study for a period of at least 30 days.
3. Child and parent/guardian request additional time to consider treatment options.
4. Changes in healthcare insurance that require clarification before additional testing/interventions are initiated.
5. Children currently on a “burst” of oral corticosteroid therapy for asthma may be enrolled, but PSG and daytime measurements may not be done until after daily oral corticosteroids are no longer prescribed and 30 days have passed since the last dose. Children using chronic steroids for asthma do not need to be deferred.
6. Children with a comorbidity that is considered to be contributing to MSDB (e.g., untreated allergic rhinitis) for which the otolaryngologist recommends treatment and re-evaluation.

5. Participant Recruitment and Consent

5.1. Participant Recruitment

Children with MSDB will be recruited from the Sleep Clinics, Sleep Laboratories, Otolaryngology Clinics, Asthma Clinics and general pediatric clinics at each clinical site. Where available, real-time alerts in the electronic health record will also be used.
The sources of referral, approaches for recruitment, and recruitment procedures will differ somewhat among the sites based on local variation in referral patterns and the organizational working relationship between the principal investigators and other specialties. At every site, recruitment procedures, including regular review of electronic medical records and upcoming clinic appointment schedules, will meet the local HIPAA and Institutional Review Board (IRB) requirements specific for that site.

Recruitment sites will utilize local web sites, newsletter, organizational communication channels and EMR-based tools to assist with identifying potential study candidates. The Clinical Research Center will speak to patients and if interested will refer them to Research Coordinator on the PATS Study team weekly via email. The general procedures to be followed at all sites are:

- Children referred to ENT, sleep clinics/labs or other clinics who are potentially eligible (i.e., by age range, referring diagnosis, lack of comorbidities) will be identified by review of EMR at least one week prior to the visit.

- Prior to the scheduled clinical visit, referring physicians will be contacted to confirm appropriateness of study participation for each potential participant and to agree to allow study personnel to contact the family.

- Where available, some children will be referred by their primary care provider using the electronic medical record real time alert.

- Families of potentially eligible participants will be contacted (either in person at the time of their clinic appointment or by telephone with arrangements made for

a subsequent interview if needed). The study will be described and written informed consent obtained. Following consent, a standardized set of screening questions will be administered to further assess eligibility criteria as per the screening (Child Information Worksheet) case report form (CRF).

- Children who meet initial study eligibility criteria who have not already had a standardized PSG within the previous 60 days (i.e., most of the children recruited from ENT clinics or general pediatric offices) will be invited to have a research PSG. The PSGs performed as part of routine clinical care for the other children will be obtained and scored centrally to confirm that PSG eligibility criteria are met.

5.2. Overview of Procedures

Once potential participants are identified, the following general procedures will be used in preparation for the informed consent discussion:

1. Families of potentially eligible participants will be contacted by telephone and/or during the clinic or sleep lab visit, if applicable to ascertain interest. Each site will utilize an IRB-approved telephone script to invite families and participants to consider enrollment into the study.

2. A preliminary eligibility determination check list (Child Information Worksheet) will be utilized and completed for potentially eligible participants.

3. A preliminary Screening and Prescreening Summary form will be completed at each site on a bi-monthly basis to tracking recruitment efforts and activity

4. A screening visit to explain the study protocol in detail and obtain informed consent will be conducted. *Note:* This visit may coincide with the ENT, PSG or other clinical visit at the discretion of the family and research team.

Procedures to confirm eligibility after the informed consent discussion

1. Participants who have not been evaluated by ENT for surgical eligibility within the prior 90 days will be referred to the ENT clinic as a research visit for evaluation of surgical candidacy. During their surgical evaluation, children will be evaluated for concomitant ENT issues which could exacerbate their symptoms of obstructive sleep-disordered breathing. If such conditions are identified, study enrollment will be deferred until the condition is treated per routine clinical practice. The child will then be re-evaluated and a determination made at that time if study participation is appropriate.

2. If initial eligibility criteria are met and informed consent is given, then :
    - Prior PSG data (performed for clinical purposes within 60 days of the baseline/randomization visit) will be transmitted to the Reading Center to ascertain PSG eligibility OR

- A research PSG will be scheduled to be performed locally and scored centrally by the Reading Center

3. PSGs will not be scheduled or occur within 7 days from the time of:
    - a febrile illness
    - upper respiratory illness resulting in increased coughing
    - acute nasal problems
    - asthma exacerbation

4. The centrally scored PSG report will be transmitted from the DCC/Reading Center to the clinical site where it will be imported into a study eligibility file. Based on the PSG findings, ENT evaluation and initial eligibility criteria, preliminary eligibility will be determined. Families will be contacted, consent will be re-affirmed, and the baseline visit will be scheduled. *Note:* Children with PSG results that exceed the AHI or desaturation criteria after central review are ineligible for participation regardless of the local clinical interpretation of the PSG data.

5. Baseline and follow up visits will aim to collect data representative of the child's usual health status. Thus, PSG, baseline and follow up visits will not occur earlier than 30 days from the time of an acute exacerbation of illness requiring hospitalization, or oral steroid medication "burst". When a child has other symptoms such as a fever or nasal/respiratory illness, then the baseline and follow-up visits/exams *excluding PSG* (see stipulations above) will not be scheduled or occur within 14 days from the time of a febrile illness.

5.3. Informed Consent

Each clinical center will be responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its IRB. Informed consent must be obtained (signed and dated by the participant's parent/guardian) prior to initiation of any study related activity. At the time of screening, written consent for parental permission for the research will be obtained. In addition, assent will be obtained from each participant 7 years of age or older in the presence of the parent/guardian when required by a clinical site's local IRB.

Clinical sites will prepare an informed consent form following the guidelines of the central IRB and all applicable local hospital and regulatory requirements for Informed Consent. The form will, at a minimum, contain a description of the purpose of the research, description of procedures at each study visit, expected and potential risks, benefits, burden, participants' rights and alternative treatments.

Consent from the parent/guardian will be obtained at the time of study entry in the presence of one of the investigators; assent will be obtained from the child him/herself if required by the local IRB, in the presence of the parent/legal guardian. Prior to the signing of the informed consent, all aspects of the study will be explained in detail and the research team member will review the details of the consent form verbally with the parent/guardian and answer any questions they may have concerning participation in the

study. They will be informed of the nature of this research, its potential benefits, and possible risks. It is stressed that participation is voluntary. The family 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. A physician-level member of the study team will be present to answer questions during the consent discussion, and members of the research team will be available to answer questions throughout the study. The original signed IRB-approved consent form will be kept in the participant's study file at the clinical center and a copy of the signed consent form will be given to the family.

If parents of subjects are CHOP employees, they will be informed that their participation will not affect their performance evaluations or employment, and that the study data/questionnaire responses will not be shared with their supervisor.

The following compensation plan pertains to participants enrolled at CHOP. Each individual site's compensation plan is provided in their reliance site survey.

During the clinic visit, the research coordinator will explain the following compensation plan.

- The parent/caregiver accompanying you to the visit will receive $50 cash/check or ClinCard for each sleep study performed, as a reimbursement for transportation, parking, meals, and baby-sitting costs for siblings.
- The parent/caregiver accompanying you to the baseline day visit will receive $25 cash/check or ClinCard as a reimbursement for transportation, parking, meals, and baby-sitting costs for siblings.
- Your parent/caregiver will receive $25.00 cash/check/ClinCard for the remote 6 month.
- The parent/caregiver accompanying you to the visit will receive $74 in cash/check or ClinCard for the 12-month day visit as a reimbursement for transportation, parking, meals, baby- sitting costs for siblings and for the time involved in the phone calls.
- Your parent/care giver will receive $50 cash/check or ClinCard in trust for you as compensation for your time and effort for every visit involving a sleep study, and the baseline day visit.
- Your parent/caregiver will receive $100 cash/check or ClinCard in trust for you as compensation for your time and effort at the 12-month day visit.
- You will also get small "prizes" (stickers, toys of < $ 10 value, etc.) during the visits.

Education in the protection of human research participants is required for all research team members and includes certified completion of the research compliance course "The Collaborative Institutional Training Initiative (CITI) Course in Human Research Subject Protections" or equivalent local courses.

5.3.1. HIPAA Authorization

Following mandated federal HIPAA regulations and according to local IRB guidelines, the use and disclosure of the subject's protected health information will be explained and participant authorization will be obtained. The consent and/or authorization forms will list those individuals and organizations that may have access to the participant's research data.

Other elements of authorization must include: the use of protected health information in future studies (for example, storage of blood samples for future analyses other than that which is listed in the protocol at the time the informed consent was obtained) and the participants' right to withdraw permission and have the blood samples destroyed. The consent and/or authorization forms must also state that investigators will have the right to reject participants from the research trial if written authorization is not provided. At each clinical site, the process of participant recruitment must be reviewed and approved by the site's local IRB to help assure that privacy protections are consistent with federal HIPAA regulations.

The following information will be explained to families during the informed consent process:

> Some of the questionnaires are scored by commercial companies involved in developing these types of behavioral tests. The ratings you enter on these questionnaires will be sent electronically to the companies for scoring. The companies will not have information about your child other than your child's age, sex, and the date that the questionnaire was sent. You child's birth date will also be sent to the company that scores one of the questionnaires. However, no other personal information that could identify your child will be shared with these companies.
> Some companies may use summary information from these tests, such as helping them develop better tests or scoring procedures. However, individual information on your child will not be used for any commercial purpose.

5.3.2. Patient Confidentiality

All participants are recruited and followed at the participating clinical centers. To maintain patient confidentiality, participants are identified to the DCC only by patient identification numbers and no personal information will be transmitted to the DCC. Furthermore, data for reports and publications will be provided in aggregate or blinded form without the identification of individual patients.

Families will be informed during the informed consent process that the limited PHI noted in section 5.3.1 is submitted to online companies for the scoring of neurobehavioral measures.

All information will be kept strictly confidential and used for research purposes only. All research data will be collected on standardized research forms with participant identification numbers, but without personal identifiers.

Procedures to assure confidentiality will be strictly observed. The clinical sites and participating centers will follow standard guidelines to assure that participant confidentiality is maintained. All data will be:

- kept in confidential locked files
- identified by participant identification number only
- kept separately from identifying information used for participant tracking and follow-up contacts.

Computer files do not permit linking individual data with medical or other data collected for research purposes. Identifying information will be kept in separate locked files. No identifying information will be disclosed in reports, publications, or presentations.

6. Risks and Benefits to Participants

6.1. General Statement about Risk versus Benefit

In most clinical trials evaluating a more intensive versus a less intensive intervention, one expects that the more intensive treatment (in this case AT) may have both greater efficacy and increased risk, which must be assured to be in a favorable balance. Participants will be closely monitored during the study and will be monitored by a Data Safety Monitoring Board (DSMB) and an external safety officer.

6.2. Potential Risks

Participants eligible to participate in the study are being clinically evaluated for habitual snoring, have MSDB confirmed by PSG, and are all potential candidates for AT from an experienced ENT surgeon as part of their usual clinical care. *Thus, the risks of having surgery and anesthesia as part of this study are the same as the risks of having these procedures outside of the study. However, participants are being randomized in this study, which is a departure from usual care that may expose participants to different risks."*

Note that potential participants with obstructive sleep apnea are excluded from participation.

Risks of deferred treatment

The potential consequences of untreated MSDB may include behavioral problems, sleep disturbances, impaired quality of life and hypertension. However, it is not known definitively whether these symptoms and signs are related to MSDB or not, and if they are cured by AT; hence the purpose of this study. The 12 month wait, however, appears small relative to the average, 3.3 years (range, 6 months to 13 years) that elapse between the onset of significant OSAS symptoms and AT[70]. Further, many children referred for clinical evaluation for MSDB may wait months for an ENT clinic appointment, have a further wait for a PSG if scheduled, or a further wait for surgery. It is reassuring to note that the CHAT study, which evaluated children with a more severe form of SDB

(i.e., OSA), showed no cognitive or cardiovascular changes over 6 months of watchful waiting. In the CHAT study, which involved children with more severe SDB, only 9 of 464 (1.9%) children were designated as treatment failures, i.e., having worsening of symptoms requiring a cross-over of study arms. No child in the CHAT study had any serious complications attributed to treatment delay, such as developing failure to thrive, respiratory distress or cardiac complication[3]. As described in the protocol, specific safeguards will be followed to ensure the participant's safety, and the participant will have close follow-up by telephone, email and/or text messaging, and in-person visits. Regular monitoring for adverse events will provide a mechanism for referring the child for evaluation for earlier surgery, if so recommended by the external Medical Monitor.

Risks of adenotonsillectomy

AT is a commonly performed operation, with clear standardization of approaches. Although associated with a finite mortality and small morbidity, levels of risk are those which the participant would have been exposed to as part of usual care. Monitoring of surgical outcomes according to the Surgical Quality Control Manual of Procedures will be implemented by the University of Michigan.

Surgical complications associated with the study can occur in the peri-operative period, or in the months following surgery. Most of the following risks are rare, as can be seen from the site-specific data presented below. Older data (1970's) indicated a mortality rate for tonsillectomy of 1:16,000 to 1:35,000[2;42]; the current mortality rate is likely lower, and even lower in otherwise healthy children ≥3 years of age without major comorbidities.

Perioperative Risks (within 24 hours): damage to teeth, infection, trauma or burns to soft tissue, atlanto-axial subluxation with neurological deficit, foreign body aspiration, airway fire, excessive blood loss (≥ 7 ml/kg), need for blood transfusion, hemorrhage that requires transfusion or an intervention to control, airway obstruction, re-intubation requiring unanticipated ICU admission, death and other related perioperative complications.

Post-operative Risks: dehydration; which may require intravenous fluids or inpatient admission, hemorrhage; which may require in-patient observation admission or return to the operating room, nasal regurgitation requiring speech therapy or surgical intervention, hypernasality requiring speech therapy or surgical intervention, nasopharyngeal scarring or stenosis which may require surgical intervention, carotid pseudoaneurysm, cervical osteomyelitis, refractory torticollis, regrowth of tonsil or adenoid tissue and other related long-term surgical risks.

Risks of Anesthesia: Common side effects of general anesthesia include nausea, vomiting, and a sore or painful throat following surgery. Serious general anesthesia-related complications, though rare, can include breathing difficulties, drug reactions, changes in blood pressure or heart rate or rhythm, heart attack, or stroke. Death or serious illness or injury due to anesthesia is very rare and is estimated to be 1:250,000 in healthy children (data provided by the IRB Committee).

The children at the highest risk for complications of AT are those less than 3 years, those with significant comorbidities and those with severe OSAS[7]. All those high-risk

groups will be excluded from this study. In the CHAT study, which was performed in a population similar to the current one (except with more severe SDB), 221 children underwent AT. Of those, 11 (5%) returned to the Emergency Department after discharge due to fever, dehydration, or bleeding. 7 (3%) of these children were readmitted (4 with bleeding). 2 children (0.9%) returned to the operating room for cauterization and both were discharged the following day.

The parent/legal guardian(s) of all study participants will be informed of the surgical risks at the time of consent for the study. The surgical team will also review surgical risks with the parent/legal guardian (s) at the time of consenting for surgery.

Mortality and Morbidity of Adenotonsillectomy by Site

At Children's Hospital of Philadelphia, we prospectively followed 329 children who underwent AT at the Main Hospital following abnormal PSG from May 2012 to May 2013 (IRB #12-009230). In contrast to the current study population, which is older and does not have major comorbidities, this was a very high-risk population, with 27% being < 3 years of age, 43% having comorbidities, and a mean apnea hypopnea index of 19.5/hr. Nevertheless, despite the complexity of the study population, there were no deaths, only 1 child (0.3%) required reintubation, and 2.4% had either early or late bleeding requiring surgical intervention.

At University of Michigan Medical Center, the rate of post-operative bleeding averaged 2.0% over the past 5 years, with no reported instances of persistent velopharyngeal insufficiency, nasopharyngeal stenosis, or death during this time.

At University of Texas Southwest Children's Medical Center, based on over 2,000 annual pediatric tonsillectomies in children < 12 years of age over the past 3 years, the rate of primary post-tonsillectomy hemorrhage was 0.2%, secondary post-tonsillectomy hemorrhage 2.3%, dehydration requiring admission 1% and other causes for readmission 0.2%, with no mortality.

At Rainbow Babies and Children's Hospital, Cleveland, statistics are available for the past year. The rate of post-operative hemorrhage was 1.4%, with no mortality.

At Boston Children's Hospital, Boston, mortality is 0%.
Morbidity overall rate for the past 2 years is 6.4%

At Children's Hospital of The King's Daughters, Norfolk , mortality is 0%.Morbidity rate for bleeding post T&A necessitating return to OR or admission or ED observation was 2.2%

At Cincinnati Children's Hospital, Cincinnati: Mortality- 0%
Morbidity- bleeding post tonsillectomy requiring ED visit or readmission – 1.7% 2017
Morbidity- bleeding post tonsillectomy requiring ED visit or readmission – 1.2% 2016
Morbidity- Admission for dehydration without bleeding 1 – 0.8% 2017
Morbidity- Admission for dehydration without bleeding 1 – 1.2% 2016

6.3. PSG Risks

No serious risks are encountered from polysomnography, which is a standard, noninvasive monitoring procedure. Sleeping away from home may be unsettling. To allay anxiety, the participant's parents/guardians will be encouraged to stay overnight in the same room as the participant. Sensors and tape may cause transient skin irritation.

Physical examination and anthropometry risks

There are no risks associated with physical examination or anthropometry, although blood pressure measurements may be transiently uncomfortable.

Risks with urine collection

There are no risks with urine collection. As the specimen need not be sterile, the participant can urinate into a "hat" container placed over the toilet.

6.4. Risks Identified in Behavioral Testing

Completing these measures may be anxiety-producing; these risks will be addressed by providing an appealing and quiet private area to complete the measures. All data will be kept confidential. The surveys do include questions regarding suicidality. If at any time during the assessment there is concern that a participant has suicidal ideation, the study team will immediately evaluate the participant. If the participant is felt to be a danger to themselves or others (via specific questionnaire responses or spontaneous reports from participant or parent), a study team member will escort them to the emergency department for further evaluation and management. Indications of child abuse will be followed up through notification of the hospital child abuse team and/or state authorities, as appropriate at each site.

6.5. Phlebotomy risks

Phlebotomy may result in transient pain, bruising or dizziness, as well as anxiety. There is a theoretical risk of phlebitis or infection which is uncommon. Phlebotomy will be performed by skilled pediatric research nurses, and a topical anesthetic will be offered to the participants. Families refusing phlebotomy despite encouragement will be allowed to participate in the rest of the study.

6.5.1. Burden to participant

PSG visits and daytime study visits will be scheduled during a time when children are stable and free of acute illnesses. Testing of neurocognitive/behavioral functioning is performed with regularly scheduled breaks during test administration to avoid excessive fatigue.

6.6. Potential Benefits to Participants and Others

There is prospect for direct benefit to participants, although it is possible that some or all participants will not receive direct benefits. Based on the nonrandomized smaller studies in children with MSDB, and the CHAT study on children with OSA beginning with an apnea hypopnea index as low as 2/hr, participants randomized to eAT may show

improvements in behavior, sleepiness and quality of life. It is also possible, based on adult data, that in children with MSDB, treatment will lower their cardiovascular risk profile[21]. Please see the rationale and Significance sections for a detailed description of the rationale for AT in improving behavior, sleepiness and quality of life in children with MSDB.

Participants randomized to WWSC may benefit by avoiding surgery if snoring and symptoms resolve without surgery or if the study shows that surgery does not improve behavioral outcomes.

In addition, all participants will receive information about healthy sleep habits for children. Children identified with obstructive sleep apnea during PSG may benefit from being screened for this study, but will ultimately be excluded from participation. Data collected for research purposes only (research PSGs, behavioral performance testing, behavioral rating scales and IgE level) will be made available to families, and the child's physicians after the study ends and may provide beneficial baseline information for future health concerns. Any data indicating a health risk will be made available to the child's physician as soon as those data are reviewed. The information obtained from this study will improve our understanding of the effects of MSDB on children's health, and will lead to better management, which is important as currently the management of MSDB varies widely across the country.

6.7. Alternatives

A discussion of alternative treatments (non-participation, other treatments available, and AT at the discretion of the ENT surgeon) will be presented at the time of informed consent.

7. Study Interventions

All participants, regardless of treatment assignment (eAT or WWSC) will receive the following interventions throughout the course of the trial:

7.1. Sleep and Healthy Lifestyle Education

Educational material on healthy sleep habits will be provided to each participant at the baseline visit after research data are collected. Standardized materials recommended by the National Institute of Health and pediatric professional sleep societies will be used to reinforce optimal sleep healthy and educational play will also be encouraged by providing take-home materials.

7.2. Other Supportive Care

At initial evaluation (and as needed throughout the course of the trial), participants identified by the site principal investigator as having suboptimal asthma or allergy control will be referred to their primary care physician for management and further treatment of these problems.

8. Procedures Specific to Treatment Arm Assignment

8.1. Surgical Treatment – Early Adenotonsillectomy (eAT)

Within 1 to 4 weeks of randomization, participants randomized to the eAT arm will undergo AT under general anesthesia, as occurs as part of usual care. Surgery will be performed by board-certified otolaryngologists with or without the assistance of resident physicians in accredited otolaryngology training programs.

Prior to the surgical procedure, tonsillar size will be graded using a standardized scale of 0-4 as described above. Extent of adenoid tissue will also be graded as mild (0-33%), moderate (34-66%) or severely (67-100%) obstructing the posterior choanae. Complete bilateral tonsillectomy and removal of obstructing adenoid tissue will be performed by cold dissection, monopolar electrocautery or any other recognized surgical technique. Further details of surgical intervention and quality monitoring of surgical intervention will be outlined in the Surgical Quality Control Manual of Procedures.

8.2. Participants Randomized to Watchful Waiting with Supportive Care

After 12 months, children who did not get surgery who have a 12-month PSG showing obstructive sleep apnea (apnea hypopnea index >or =3.0 /hr or obstructive index > 1/hr) or whose parent reports ongoing symptoms/concerns will be referred back to ENT for further clinical management (such as adenotonsillectomy) as per standard clinical care.

9. Study Procedures

A study visit schedule is provided in Appendix A. Visit time points, study procedures and assessments are listed in the order in which they occur.

9.1. Polysomnography (PSG)

All children will undergo standardized screening PSG at study entry to determine eligibility, and at the 12 month visit.

9.1.1. PSG Methods Overview

Each clinical site will use a standardized approach as established in training. Existing laboratory equipment will be used, but data will be standardized by using the same montage and similar sensors, sampling rates and filters. Sleep technicians who collect PSG data for this study will be supervised by a lead technician who was certified by central training for technical proficiency to collect research PSG data for this trial, or someone trained by a centrally certified technician. 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 as a standardized European Data Format (EDF) file and electronically transmitted to an FTP server at the central Reading Center for standardized scoring.

9.1.2. Screening PSG

All potential participants who meet the initial eligibility criteria will be evaluated through a standardized PSG prior to the baseline exam. PSG results that do not meet AHI/saturation criteria after central review by the Reading Center are ineligible for participation regardless of the local clinical interpretation of the PSG data and the baseline visit will not be scheduled. Baseline PSG data can be obtained in two ways:

1. A proportion of PSGs may have been performed as part of routine clinical care. PSG data (performed for clinical purposes within 60 days prior to the baseline/randomization visit) will be transmitted to the Reading Center where they will be re-scored to ascertain PSG eligibility and entry into the study. If a clinical PSG has been performed more than 60 days prior to baseline/randomization or was not performed using agreed upon research sensors and montages, then a research PSG must be performed.

2. Potential participants who have not undergone a PSG within 60 days prior to the baseline/randomization visit will undergo a research PSG. Resulting PSG data will be transferred to the Reading Center within 48 hours to determine PSG eligibility and to collect research quality data.

9.1.3. 12 Month Endpoint PSG

2 weeks before or 2 weeks after the scheduled Month 12 daytime visit, all participants will undergo a research PSG. Data will be transmitted to the Reading Center and results will be scored (refer to the PSG Manual of Procedures).

9.1.4. Scheduling the PSG

One to two days prior to each scheduled PSG, families will be contacted to remind them of the visit and to ensure that intervening medical illnesses have not occurred, requiring the visit to be rescheduled. These include any of the following within the previous 7 days:

- febrile illness
- upper respiratory illness resulting in increased coughing
- acute nasal problems
- asthma exacerbation

9.1.5. PSG Procedures

Children will be encouraged to maintain their usual daily routine prior to PSG. Lights off will be at approximately 2000 -2100 (depending on age) and lights on no earlier than 0600. Neither sedation nor sleep deprivation is used to induce sleep.

9.1.6. Montage

The following are monitored: Sleep architecture (6 EEG sites [F_3/M_2, F_4/M_1, C_3/M_2, C_4/M_1, O_1/M_2, O_2/M_1], bilateral electro-oculograms [EOG: ROC/A_2, LOC/A_1], submental electromyography [EMG]; airflow by oronasal thermocouple (Pro-tech);

nasal pressure cannula (Pro-tech); snoring sound (microphone by Pro-tech, a vibration flow sensor, or a battery operated Tascam microphone; respiratory effort (chest and abdominal wall inductive plethysmography); end-tidal CO_2 (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.

- When possible, EEG, EMG, and EOG signals will be sampled at rates designated as "desirable" by The AASM Manual for the Scoring of Sleep and Associated Events Version 2.2 (EEG, EOG, EMG, ECG and snoring at 500 Hz, respiratory signals at 100 Hz, and oximetry at 25 Hz).
- When equipment precludes collecting data at "desirable" rates, all data must at least meet the AASM 2015 "minimal" sampling rate criteria (EEG, EOG, EMG, ECG and snoring at 200 Hz, respiratory signals at 25 Hz, and oximetry at 10 Hz).

9.1.7. Central Transmission of PSG Data

The PSG will be exported in EDF format and transmitted to a sFTP server at the Reading Center for standardized scoring within 2 business days. If PSG urgent referral criteria are identified (i.e., on baseline/screening PSG, severe levels of obstructive sleep apnea precluding randomization; or on follow-up PSG, levels that exceed adverse event thresholds), the data will be reviewed by the Reading Center Director. An Urgent Referral Alert form will be completed and transmitted to the clinical site for follow-up. The clinical site will provide this information to appropriate physicians and family members for clinical follow up (refer to PSG Manual of Procedures).

9.2. Study procedures and details of the baseline visit

Following confirmation of initial eligibility including screening PSG, participants will be scheduled for a baseline morning visit with consideration for any intervening medical illnesses (30 days from the time of an acute exacerbation of illness requiring hospitalization or systemic steroids or 14 days from the time of a fever or an illness of sufficient severity that it required the child to miss 2 or more days of school/pre-school or be confined to bed for 2 or more days).

Visits should aim to begin between 8:00-9:00 AM and no later than 11 AM. The evaluation will generally last no more than 4.5 hours. Participants will be encouraged to follow their usual bedtime routine the night prior to testing. Participants will undergo the following, in the order listed:

- Brief orientation to testing facility
- Urine collection for cotinine
- Resting morning blood pressures in triplicate
- Anthropometry
- Brief physical examination by the study physician or designee
- Breakfast/snack and rest period
- Behavioral performance testing by child and questionnaire completion by parent
- Brief rest period

- Venipuncture (note: fasting not required)
- Randomization

The Research Coordinator will also review and provide an appointment schedule and reaffirm the importance of maintaining the blind.

9.2.1. Orientation

On arrival to the research facility, participant and parent/legal guardian (s) will be introduced to the research staff and provided with a brief tour of the facilities, using child-friendly approaches.

9.2.2. Urine collection for cotinine

The child (with the assistance of the parent) is instructed to void into a collection device (urinal, “hat”, or bedpan). Study staff transfers the specimen to a non-sterile container. Following instructions outlined in the Laboratory MOP, the specimen is stored locally at -80°C and shipped on dry ice to the central laboratory at Children’s Hospital of Philadelphia Clinical and Translational Research Center as per the schedule in the Manual of Procedures.

9.2.3. Morning blood pressure

After a 5 minute rest period, while the child is sitting, systolic and diastolic BP will be measured 3 times, at least 60 seconds apart, according to standardized guidelines. Cuff size will be determined by measuring the circumference of the upper arm, measured at the midpoint, and identifying the appropriate bladder size from a standard chart

9.2.4. Anthropometry

Parent/caregiver will be instructed to have the child wear loose clothing to the visit. Weight (to 0.1 kg) will be measured on a calibrated digital electronic scale. Standing height (to 0.1 cm) will be measured with a stadiometer, and neck, waist and hip circumferences will be obtained to determine regional fat distribution, as outlined in the Anthropometry MOP. Measurements will be repeated three times, and average values will be utilized, as defined in the MOP.

9.2.5. Physical examination

The Principal Investigator/designee will review the participant’s medical and sleep history and perform a brief standardized physical exam, including standardized assessment of tonsillar size, evaluation of the oropharynx using Friedman and Mallampati position scales, and identifying any abnormalities on heart, lung, neurological and ears, nose and throat assessments.

9.2.6. Breakfast/Snack and rest period

The child will be provided with a snack and a brief break.

9.2.7. Behavioral performance testing and questionnaire completion

Behavioral performance testing will take approximately 20 minutes for the child and questionnaire completion will take approximately 90 minutes for the caregiver. Testing will be administered by a Research Coordinator who is centrally trained, certified by the Neurobehavioral Quality Control Committee, and blinded to the treatment arm. Tests will be performed in the same order. 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. The parent will complete the questionnaires in a separate room while their child is being tested, on a computerized system. The child will be supervised in a hospital play room, with a Child Life therapist, or other appropriate site and personnel, while the parent completes the surveys. All tests will be performed as outlined in the Behavioral Testing MOP. The Research Coordinator will be available for assistance, and will ensure completion of all tests at the end of the session.

We will provide families with paper forms that can be mailed or emailed back to the study coordinator. Blinded 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 with a blinded RC. These alternatives meet CHOP IT standards and are critical to have a complete dataset in all participants.

Child Performance Testing

- NIH Toolbox 9-Hole Pegboard Dexterity Test (a test of fine motor coordination)
- Go-No-Go Continuous Performance Task (GNG), a test of sustained attention (vigilance).
- PedsQL: Children $\geq$ 5 years of age also complete the child version of the PedsQL, a generic measure of global quality of life

Parent Questionnaires (note that several measures utilize a date stamp when questionnaires are entered electronically into the commercial scoring websites)

- Behavior Rating Inventory of Executive Function (BRIEF2/P), a measure of executive function (the global score a co-primary outcome). The BRIEF-P is for use in pre-school children.
- Child Behavior Checklist (CBCL), a measure of behavior
- Conners Third Edition Short Form, a measure of attention-deficit/hyperactivity disorder symptoms (parents of children $\geq$6 years of age only)
- Adaptive Behavior Measure System, 3rd Edition (ABAS-III), a measure of children's everyday functioning (this measure is centrally scored, and date of birth as well as date of study and study ID is required to be entered into the WPSpublish website)

- Epworth Sleepiness Scale modified for children, a measure of daytime sleepiness
- Pediatric Quality of Life Inventory (PedsQL; parent form), a generic measure of global quality of life
- OSAS-18, a measure of disease-specific quality of life
- Pediatric Sleep Questionnaire Sleep-Related Breathing Disorder Scale (PSQ-SRBD scale), a measure of symptoms of SDB, including nighttime and daytime symptoms.
- Family Assessment Device, a measure of family functioning
- Parenting Style Questionnaire, a survey of the type of parenting style
- Parenting Stress Index 4th Ed., Short Form, a measure of parents' perception of stress
- Rapid Estimate of Adult Literacy in Medicine, Revised, a measure of patient (caregiver) health literacy (only at baseline visit)
- Experiences of Discrimination, a measure of experiences with racism
- International Study Of Asthma And Allergies In Childhood (ISAAC), a survey to determine the presence of asthma, rhinitis and eczema
- Asthma Severity Survey, a measure of asthma exacerbations and controller therapy based on items from the Composite Asthma Severity Index (only for children with ISAAC Global Wheezing Score $\geq$5)
- COVID-19 Survey

9.2.8. Venipuncture for IgE

Approximately 5 cc of blood will be obtained by venipuncture (and no more than 3 cc/kg body weight) and after preparing the skin with a local anesthetic, per participant preference. Within one hour of collection, the specimen is centrifuged and serum and plasma aliquoted, with removal and storage of the buffy coat if applicable. Following instructions outlined in the Laboratory MOP, the specimen is stored locally at -80°C and shipped on dry ice in batches as per the MOP to the central laboratory at Children's Hospital of Philadelphia Clinical and Translational Research Center. This sample does not require fasting and may be collected at another time point within 30 days of the baseline visit, per participant preference.

9.2.9. Medical status

The Research Coordinator will obtain baseline information regarding health status and medication according to a standardized script, and enter responses into the CRF.

9.2.10. Sleep educational material is reviewed.

9.3. Randomization

Participants meeting all eligibility criteria will be randomized at the end of the Baseline Visit to either the eAT group or to WWSC. The unblinded 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 (e.g., stratification variables) 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 baseline 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 based upon the subject criteria. The DCC will be responsible for providing and documenting appropriate user access to the database, preventing against unauthorized entry into the randomization system.

Participants will be assigned randomly to either eAT or WWSC. For those participants assigned to the eAT arm, arrangements will be made by the unblinded coordinator to schedule surgery within 4 weeks of randomization.

9.4. Teacher report forms

BRIEF2/P, Conners 3 Short Form and Teacher Report Form (teacher version of the CBCL) will be mailed to pre-school and schoolteachers. The teacher (or for summer months, the teacher from the preceding semester) will be mailed the forms along with a background letter on the study, written permission to contact them signed by the parent and a gift card as an incentive. Repeat mailings, and if needed phone calls, will be made if forms are not returned within 2 weeks. At each subsequent visit, caregivers will also be asked to bring in the child's most recent report card so that school absences and grades can be recorded and used for exploratory analyses. The teacher ratings will be obtained at baseline, Month 6 and Month 12. Permission to contact the child's primary or homeroom teacher will be obtained from parents at the time of consent, and again at the time each follow-up visit is scheduled.

9.5. Monthly caregiver interviews

As part of ongoing contact with participants (see Appendix A Visit Schedule), caregivers will be contacted on a bi-monthly basis for completion of check in questionnaires and surveys. Centrally trained research coordinators will administer these questionnaires by telephone, email and/or text messaging at months 2, 4, 6, 8, 10 and in person visit at 12 months. A structured interview that will 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. The coordinator will use a script with follow-up questions and record all information in the CRF.

If parents cannot be reached by phone for monthly calls, we will provide parents direct links to The SLICE data management system provided by The DCC. However, adverse

events and healthcare utilization will be followed up by phone calls as there are many nuances that need direct communication with the coordinators.

On alternate months of check in questionnaires, caregivers will be contacted to assess for adverse events and health care utilization only.

9.6. Health care utilization (HCU) and electronic medical record (EMR) surveillance

EMR will be tracked by both monthly manual review of EMR by the Research Coordinator after each reported adverse event or HCU event, and by automated surveillance of billing records and pharmacy records using query systems co-developed by Dr. Linden, conducted approximately bi-annually. At each monthly check-in by telephone, email and/or text messaging, or in-person visit, the research coordinator will conduct a structured interview that will 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. Data will be entered into a CRF. In addition, each health system's billing system informatics analytics team will extract relevant information from inpatient, outpatient and pharmacy records as outlined in the DCC application. Query results will be returned monthly to the research coordinator who will extract the information to the CRF and compare these data to the parent-reported data. When discrepancies are identified, the research coordinator will attempt to resolve differences by further interviews with the caregiver, requests to other health institutions for medical record release, or by consulting with the DCC. Healthcare utilization data will be collected prospectively through ongoing surveillance of electronic medical records (EMR) for up 24 months following randomization of subjects. 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.

9.7. Study Visits (see Appendix A for Summary of Visit Schedule and Procedures)

The details of the specific study procedures at each study visit are summarized in the previous section. This section lists the study visits and summarizes the procedures at each visit.

9.7.1. Screening visit/PSG eligibility – Day -60 to -1

At this visit, preliminary study eligibility is confirmed and informed consent obtained. If the participant had a clinical PSG, then these data are sent to the DCC/ Reading Center to confirm eligibility. If the participant has not had a PSG, then a research PSG is performed.

9.7.2. Baseline visit – Day 0

After PSG eligibility for MSDB is confirmed, this visit includes anthropometry, BP measurement and physical examination. The child completes behavioral performance measures and the parent completes questionnaires about behavior & attention, SDB symptoms, sleepiness, quality of life and family functioning. Children ≥ 5 years of age also complete the child version of the PedsQL. Urine is collected for cotinine and serum

IgE is collected by venipuncture. The research coordinator inquiries about adverse events, changes in health status or medication, and HCU. Eligibility is confirmed and the participant is randomized. Behavioral rating scales are mailed to teachers.

9.7.3. Monthly Check-In – Months 1, 2, 3, 4, 5, 7, 8, 9, 10, 11

Between each face-to-face visit, study staff will make contact by telephone, email and/or text messaging, with families in both groups for inquiries about adverse events, medications, and changes in health status using a study CRF. HCU is assessed and EMR surveillance completed. Participants are reminded about upcoming study visits and study participation is reinforced.

9.7.4. Remote Interim Visit – Month 6

The parent completes questionnaires about behavior, SDB symptoms, sleepiness, quality of life and family functioning. Study staff inquire about adverse events, changes in health status or medication, and HCU. EMR surveillance is completed. Behavioral rating scales are mailed to teachers. Note that with the Covid-19 pandemic, 6 month visits can be held virtually if in-person visits are not possible, focusing on parent-related questionnaires.

9.7.5. Endpoint PSG – Month 12

Participant completes overnight PSG using the same protocol as for baseline PSG.

9.7.6. Endpoint daytime visit – Month 12

This visit includes measurement of anthropometry, BP and behavioral performance testing. Parent completes questionnaires about behavior and attention, SDB symptoms, sleepiness, quality of life and family functioning. Participants ≥ 5 years also complete the child version of the PedsQL. Study staff inquire about adverse events, changes in health status or medication, and HCU. Behavioral rating scales are mailed to teachers. Participants in the WWSC arm are scheduled for re-evaluation with their ENT surgeon within 1-4 weeks if indicated.

9.7.1. Post-participation Surveys

The research coordinator will ask and verbally consent all participants to complete 3 follow up questionnaires after completion of the study via email, mail or phone.

9.8. Potential Treatment Failures

During the trial, the research coordinator may discover signs and/or symptoms that could potentially indicate treatment failure regardless of the arm assignment. “Treatment failure” is generally defined as a condition or situation that is observed during either routine interim follow-up phone calls or any study visits or clinical visits discovered in EMR surveillance, or from parent or physician contact, and indicates a potential need to change treatment. See Adverse Events section.

The research coordinator has the responsibility to:

- Identify and record these events utilizing the Treatment Stop [TSTOP] case report form (at this stage they are "potential" Treatment Failures).
- The research coordinator will notify the PI, who will make any decisions required for the participant's clinical safety. The study team will make appropriate arrangements for further follow-up/referral (e.g., back to the referring physician).
- Follow the general procedures for reporting SAEs (i.e., notify the DCC Project Manager within 24 hours of first knowledge of the event) and Complete the SAE/Treatment Failure report within 48 hours of first knowledge of the event. It will be submitted to the DCC who will forward the AE report and all supporting documents to the Medical Monitor via the data management system (Slice). Instructions for completing and submitting this information will be listed on the form and details provided in the Master Manual of procedures. Diagnostic information that will assist in the understanding of the event may b e requested and follow up reports may be necessary. Significant new information on ongoing serious adverse events should be provided promptly to the DCC.
- The Medical Monitor will determine if the event meets Treatment Failure criteria. This information, including specific reasons for failure including why a physician involved in the child's care determined alternative therapy and which alternative therapy was recommended, will be documented on the [TSTOP] CRF and entered into the data management system. If there is discordance between the PI and the external Medical Monitor, then the Medical Monitor's decision will be used for data analytical purposes. All reports of Treatment Failures will be tabulated as aggregate data and summarized monthly for review by the Steering Committee (in blinded format) and quarterly to the DSMB (or more frequently based on the trends and the Steering Committee's recommendations).

9.9. Adverse Event Definitions and Reports

9.9.1. Overview of Surveillance for Adverse Events and Safety Indices

Adverse events are monitored through several means of surveillance, as described below:

1. Families will be in contact with study staff monthly by either electronic media (telephone, email and/or text messaging) or face-to-face visits to ascertain if a new medical or behavioral condition requiring therapy or causing interference with daily activities has occurred or been diagnosed, or if any emergency room visit or hospitalization has occurred. EMR surveillance is also used to support these efforts.
2. At each visit (day 0, months 6, and 12), and during monthly check-in, data will be collected that includes changes in health status, medications, SDB symptoms including sleepiness. Also, height, weight and blood pressure data are collected during the in-person visits and can alert study staff to the need for further investigation if problem changes are discovered.
3. Surgical adverse events will be captured by an intraoperative CRF completed by the surgeon and by questionnaires completed via a telephone interview post-operatively, and by ongoing monthly contact and EMR surveillance. Refer to the Surgical MOP for details.

4. Research data will be interrogated to identify questionnaire data exceeding values that indicate an abnormality warranting further investigation.
5. All treatment failures will be reviewed by the study's Medical Safety Monitor in real time and reported to the DSMB on a quarterly basis

9.9.2. Urgent Medical Referral Criteria

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. Because the participants in this study are pre-screened to be "otherwise healthy" children, most participants who meet Urgent Medical Referral Criteria are likely to be encountered at the time of their screening PSG and will no longer be eligible to participate and will exit the study to routine or urgent health care, as appropriate.

NOTE: At the baseline visit, one of the behavioral questions asks about suicidal ideation. A positive endorsement of that symptom will lead the study team to prompt assessment, deferred participation and possibly exclusion from the study, as appropriate for the participant's welfare. CBCL for children 6 years and older, the only measure that assesses for suicidal ideation, will be completed during an in person visit by the blinded RC only.

If the following conditions are identified during the course of the study, their occurrence will generate an Urgent Medical Referral by the Site PI who will communicate with the participant's parent or guardian, and with permission, contact the child's health care provider. Some of these conditions (abnormalities of blood pressure) will be noted as usually needing confirmation with repeat testing before clinical decision making.

- Stage 2 hypertension (> 99% for age and gender)
- PSG: Desaturation to < 90% for > 2% of total sleep time OAI >20/hr. or AHI > 30/hr.
- ABAS-3 score of <60
- 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.

9.9.3. Definitions

9.9.3.1. Pre-existing 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.

9.9.3.2. Adverse Event (AE)

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 to occur in high frequency.

9.9.3.3. Expected (Anticipated) Adverse Event

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

The Office of Human Research Protection distinguishes between risks and discomforts that are related to research compared to clinical intervention and have defined new reporting guidelines as of January 17, 2007.

Since the surgical procedure (AT) is being performed as part of usual clinical care (e.g., it is not paid for as a study procedure and is performed as part of routine clinical care), all foreseeable mild AEs that are expected to occur at high frequencies as part of routine clinical care (like PSG or phlebotomy) including those associated with surgery (AT) that do not exceed threshold definitions will not be considered adverse events and will not warrant reporting, such as the following:

Associated with PSG

- Skin irritation from removal of adhesives (lasting < 2 days)
- Temporary depigmentation under area of sensor attachment (lasting < 1 month)
- Poor sleep during PSG

Associated with AT

- Post-op throat pain lasting < 21 days and not requiring intravenous hydration or unscheduled medical evaluation or treatment.

- Post-op hoarseness or difficulty swallowing lasting < 21 days and not requiring intravenous hydration or unscheduled medical evaluation or treatment.
- Intra-operative blood loss <7 ml/kg
- Post-op blood-tinged oral or nasal secretions, lasting < *72 hours*
- Velopharyngeal Insufficiency (nasal regurgitation or hypernasality) lasting < 2 months and not requiring specific evaluation or intervention

Associated with Phlebotomy

- Temporary pain, lasting < 48 hours
- Bleeding or bruising at the blood draw site not needing medical attention

Other

- Anxiety surrounding behavioral testing not requiring psychiatric attention and not interfering with completion of the protocol

9.9.3.4. 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.

Abnormal laboratory value

A laboratory abnormality should be documented as an adverse event if:

- The abnormality suggests a disease and/or organ toxicity, *OR*
- The abnormality is of a degree that requires active management; (e.g., specific treatment, more frequent follow-up assessments, further diagnostic investigation, etc.) *AND*
- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.

NOTE: Participants and their parent/legal guardian (s) will not be informed of any of the results collected and processed in the future for research purposes. These are research data only and not meant for the purpose of diagnostic evaluation. The results will not become part of the participant's medical record.

9.9.3.5. Unanticipated Problem Involving Risk to Participants or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied

- Related or possibly related to a participant's involvement in the research

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

9.9.3.6. 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. The appropriate case report form must be completed for all events in this category according to the guidelines listed in the Manual of Procedures.

9.9.4. 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.

9.9.5. Recording and Reporting Adverse Events

At each contact with the subject, the investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all adverse events should 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/legal guardian, other than those expected and identified as detailed in the MOP will be immediately reported to the site PI.

- Signs and symptoms will be graded by the Unblinded Research Coordinator utilizing a 5-grade scale as listed in the 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 the Manual of Procedures.

9.9.6. Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization (refer to manual of procedures for definition) surgery or prolonged hospitalization, should be documented and reported as a Serious Adverse Event (SAE) unless it is AT surgery occurring as a

treatment arm. 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.

9.9.7. Follow Up on Adverse Events

The clinical investigator 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 clinical investigator will record each AE outcome on the CRF according to the instructions outlined in the MOP.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.

9.9.8. 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 investigator should instruct each participant and parent/legal guardian (s) to report any subsequent event(s) that they believe may be related to participation in this study

9.9.9. Treatment Failure

This will be defined as a change in clinical status interpreted by the Medical Safety Monitor as requiring an immediate change to established clinical therapy for SDB. Operationally, potential treatment failures will be identified by the research coordinator based on interim telephone calls, emails and/or text messaging and research visits, or contacts initiated by the participant or their referring physician. Information will be submitted to the Medical Safety Monitor who will make an adjudication of the status of the participant and notify the PI who will arrange medical follow-up as indicated. Data will be subsequently reviewed by the DSMB. Note that, as the study will utilize an intent to treat paradigm, every effort will be made to continue the participant in the study, regardless of whether the participant receives clinical treatment or not.

Examples of treatment failures include worsening symptoms of SDB such as:

1) sleepiness interfering with schoolwork.

2) new academic or behavioral problems resulting in a recommendation for grade retention, special education, or counseling

3) placement on new medications for behavioral or emotional problems

4) recurrent bacterial tonsillitis defined as 3 or more episodes of streptococcal

culture positive infection occurring over a 3-month time interval. Children who have medical record documentation of 3 culture positive infections are asked to undergo a repeat throat culture after completion of the third course of antibiotics to exclude a chronic carrier state. If this test is not ordered for routine clinical purposes, it will be arranged by the study staff and paid for by the study.

Parent/legal guardian (s) who decide that they no longer want to wait 12 months for their child to be re-evaluated for AT surgery, but whose children do not meet any of the criteria for treatment failures, are not considered treatment failures. These children will be reevaluated by the ENT physician who initially evaluated them, unless they prefer to seek other medical consultation, and will be classifies as crossovers.

9.9.10. Reporting Serious Adverse Events

The clinical site is responsible for reporting SAEs to the DCC within 48 hours of first knowledge of the event by creating an Adverse Event Report in the data management system (Slice) listing participant ID, description of the event and adverse event date. Creation of this initial report will automatically notify the DCC and provide summary data for the adverse event. SAEs will be reported to the Data Coordinating Center Project Manager, the Children's Hospital of Philadelphia IRB, the DSMB Chair, and the NHLBI Program Scientist within 7 days of its occurrence. The DCC will also provide follow up reports.

After the initial summary data are entered, the Research Coordinator and DCC will complete the full Adverse Event Report, including the following information:

- Study identifier (PATS)
- Study Center ID/Research Coordinator ID
- Participant Identification Number
- A description of the event in the form of a written narrative, including relevant medical history and/or co-morbidities
- Date of onset
- Date of resolution
- Study time point during which event occurred
- Randomization arm
- Whether study treatment was altered
- Description of actions taken by PATS staff, and follow-up required
- If the event is expected and non-mild, or unexpected

The research coordinator will provide further information on the AE in the form of a written narrative. This should include a copy of de-identified diagnostic tests or information that will assist in the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the DCC.

For all unexpected events and all events that are expected and serious the Medical Monitor will be notified and provided the Adverse Event Report. Using this report the Medical Monitor will complete an Adverse Event Adjudication form that will be available to the DCC and clinical site once completed, including the following information:

- Expectedness
- Relatedness
- Severity
- Whether the event constitutes a Treatment Failure
- If the event suggests a greater risk of harm than previously recognized
- Comments and recommendations for follow-up

In addition, the site must promptly report all SAEs and unexpected, related events 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.

Upon notification from the clinical site, any serious adverse event that might reasonably be due to the study intervention will be reported to the monitoring bodies.

10. Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. *However, since the PI at each site is blinded to the treatment arm assignment, initial* screening of adverse events will be performed by the unblinded research coordinator. If the adverse event appears related to surgery, the coordinator will contact the otolaryngologic surgical co-investigator or other unblinded investigator at the site to ascertain the preliminary relationship to study participation, and coordinate follow up when applicable. The surgical co-investigator will contact the PI whenever he/she considers it medically necessary. Note that every site has a primary surgical co-investigator. If the adverse event appears not to be related to surgery, then the research coordinator will discuss the event with the PI or other unblinded co-investigator. When necessary, the DCC will notify the independent Medical Monitor for adjudication of all severe or related unexpected events for study purposes. The PI, IRB, Steering Committee, DSMB, and NIH Program Officer will be notified of all AEs, unanticipated problems, and Treatment Failures according to the reporting timeframe specified in the MOP. The PI's responsibility will include assuring that appropriate study data are communicated to the participant's family and physicians and that appropriate referrals or interventions are initiated.

Medical Monitoring will also include oversight by the Data Coordinating Center generating reports through regular assessment of the number and type of SAEs.

10.1. Medical Safety Monitor

A pediatrician who is board-certified in pediatric intensive care, pediatric pulmonology, and sleep medicine (Dr. Connolly, University of Rochester), unassociated with any clinical site, will serve as the independent Medical Safety Monitor. The Medical Safety Monitor will provide independent adjudication of unexpected and serious AEs and potential treatment failures. The Medical Safety Monitor will have access to randomization codes to make an informed decision about a particular participant. In addition to aggregate data, the Medical Safety Monitor will receive reports of all AEs that are:

- Expected and exceed thresholds
- Unexpected and Serious
- Unanticipated Problems that fit the reporting criteria

If a medical or psychological adverse event occurs that requires immediate intervention, it will be evaluated on an individual basis and study termination or recommendation regarding immediate AT surgery will be made. The Medical Safety Monitor will also evaluate both trends in AEs and Treatment Failures across the study and within each arm, as well as to confirm or refute the occurrence of specific treatment failures.

10.2. Serious Adverse Event and Unblinding of Treatment Arm

If there is an SAE, which is thought to be possibly or probably related to the coded intervention, the clinical site, when necessary for the safety of the participant, will unmask the treatment arm assignment. An explanation of the need for unblinding the treatment arm assignment must be provided to the DCC, who will disseminate the information to the various regulatory groups (DSMB, NIH) and external site PIs. Unblinding of the treatment arm assignment is anticipated to be an uncommon occurrence and is highly discouraged. An exception is made for any information identified that may pose acute health risks or would influence immediate treatment, in which case the PI will be notified immediately.

10.3. Management of Associated Adverse Events and Discontinuation of Treatment

The administration of the intervention may be discontinued at the subject's request or by the investigator, based on clinical judgment. If the subject is withdrawn from the study and participation terminated, the Study Stop CRF must be completed documenting the date study participation ended and identifying the reason. Parent/legal guardian (s) of participants who are discontinued will be instructed to report any AE experienced after treatment without delay.

10.4. Other Study Medical Monitoring and Reporting

10.4.1. Surgical Monitoring

Complications resulting from surgery will be documented at each site with use of an intra-operative data sheet and by reports obtained from the family during routine interim follow-up, supplemented by medical records, as appropriate. Major unanticipated adverse events and unanticipated problems that fit the reporting criteria will be reported (as required by institutional IRBs). The DCC will report complications from surgery to

the Surgical Quality Control Committee, the Independent Medical Monitor and to the DSMB and NHLBI. Periodically, these results will be tabulated and any significant deviations from reported national rates will be investigated. If any surgical complication is noted that exceeds expectation of usual care, or any site experiences excessive problems (as defined by the Surgical Quality Control Committee or the DSMB), Dr. Garetz, Director of the Surgical Quality Control Committee, will initiate an investigation. Actions may include ongoing monitoring, retraining, excluding the participation of specific surgeons, or excluding specific sites.

10.4.2. Severe OSA on PSG

10.4.3. Baseline

Any OSA is an exclusion for the study, so the participant with severe OSA will exit the study and the study team will facilitate appropriate clinical management.

10.4.4. Follow-Up

Data from follow-up PSGs will be available at a time when all 12 month follow up data have been collected to minimize influencing study outcomes, an approach that is standard for research data. However, an exception will occur for any information that meets the Urgent Medical Referral Criteria. Data will be shared earlier, as described above relative to baseline data.

10.4.5. Behavioral testing

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 PATS staff if the primary and backup professionals cannot be contacted. The CBCL for children 6 years old and older, the only measure that assesses suicidal ideation, will be completed in the presence of a blinded RC only.

Participant Refusals, Screen Failure, Withdraws, Discontinuation, and Missed Appointments

11. Participant Refusal

A record will be kept of all participants and parent/legal guardian (s) who are approached but refuse to participate in the study prior to signing the Informed Consent. For tracking purposes, the reason for refusal will be documented on the Screening Log.

12. Withdraw/Premature Termination

If a participant withdraws/terminates from the study prior to the 12-month visit, every effort should be made to obtain follow-up safety data which includes information on adverse events and current health status including sleep habits and surgical AEs (if applicable). The clinical site must also complete the Study Stop CRF [SSTOP] indicating the reason for termination.

13. Missed Appointments

If a participant does not keep a scheduled appointment, the missed visit (testing) must be rescheduled within two weeks.
To minimize the occurrence of missed appointments the parent/legal guardian will be provided with the following reminders when appropriate:

- Written schedule of visits during the baseline exam
- Printed card with date of next visit or contact (when appropriate)
- Phone notification within 1 to 2 days prior to the scheduled visit
- Letter via postal mail if other methods of communication fail

14. Quality Assurance

14.1. Quality Control Procedures

Quality control measures will be implemented at several levels to ensure that all centers and personnel meet and maintain comparable and high levels of technical performance. Quality Control will be optimized by multiple levels of training, monitoring and feedback activities, including central training, certification of research personnel for all specialized testing procedures. All clinical site personnel will be centrally trained and certified by DCC, Reading Center and CCC staff. The Quality Control Procedures are detailed in the MOP for each specialty group.

14.2. Centralized Training

After protocol development and printing of a final MOP, a training session will be held at the CCC in Philadelphia. Attendees will include: all key study investigators and staff (coordinators, research assistants) and leaders of quality control committees. Joint introductory sessions will be held that include review of the entire protocol and study organization and allow study personnel to become acquainted. Specifically, but not exclusively, this training will ensure that clinical personnel understand the study's goals and objectives, data collection process, all CRFs, MOPs, database software, and all applicable Standard Operating Procedures to attest that the study is conducted in a proper manner.

Breakout sessions will focus on specific aspects of data collection and database management: polysomnography; anthropometry; behavioral performance testing; safety monitoring; health care utilization ascertainment; recruitment; follow-up and retention strategies; surgical intervention; data entry and data queries; ethical issues; and special procedures for studies of children. Specific sessions will be videotaped for future references by staff. Time also will be allotted to document proficiency in specific procedures (e.g., data entry), which may require combinations of observation by the trainer and written exams.

14.3. Certification Processes

All procedures (behavioral performance testing, anthropometry, data entry, polysomnography,) will require certification of staff prior to their performance on study participants. Requirements differ per procedure, but generally include documentation of successful performance during central training and observation, possible completion of a written exam, and submission of successfully completed studies during pilot studies (meeting standards for quality and completeness when evaluated by the relevant Quality Control group or DCC). In addition, after initial certification, each technician's performance will be monitored on an ongoing basis. If a minimal number of studies are not performed in any given study period, or if studies submitted fall below threshold levels for quality, the PI will be notified and procedures for remediation be implemented (e.g. completion of additional practice studies, re-training or removal from the study).

15. Administrative

15.1. Institutional Review Board

It is the responsibility of the Principal Investigator at each clinical site to provide their IRB with all pertinent material, including a copy of the informed consent. Approval from the reviewing IRB of the informed consent form must be obtained and forwarded to the Data Coordinating Center prior to screening or enrolling any participants. The clinical site's Principal Investigator also maintains the responsibility of coordinating with the DCC and CCC in initiating protocol re-approval, notification of protocol and/or consent form changes, adverse events, and termination of the study according to the appropriate IRB requirements. A central IRB will be used (CHOP).

Direct Access to Source Documents

Investigators will maintain, on-site, in an orderly fashion, and make available to the DCC and quality assurance personnel, the following documents: the signed study protocol, amendments, informed consent documents, and approval letters from the IRB, CRFs, all primary source documentations, and all letters of correspondence.

15.2. Record Keeping

15.2.1. Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, digital pictures, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

15.2.2. Case Report Forms (CRF)

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 PATS study portal (patstrial.org). Study-designated personnel from each site will be trained in Case Report Form completion and entry into the Data Management System.

15.2.3. Record Retention

It is the investigator's responsibility to retain study essential documents for at least 7 years after the study is discontinued.

16. Data Management and Analysis

Details of data management and quality assurance are outlined in the DCC application. The DCC will coordinate all PATS data management activities including CRF collection, entry, verification, validation and query resolution of data. The DCC will develop and maintain a computerized Data Management System for this protocol that will be deployed within each of the clinical sites. CRFs will be available to be printed locally at the clinical site from Portable Data Files (PDFs). Originals of these forms will be retained by the clinical sites. Single data entry will be performed at the clinical sites utilizing the Data Management System tools available on the workstation. A sample of data will be double data entered by the DCC for verification. 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.

16.1. Study Monitoring, Auditing, and Inspecting

16.1.1. Recruitment and Retention Monitoring

The DCC and the Recruitment and Retention Sub Committee will monitor recruitment activities, develop recruitment brochures, tools and incentives that will enhance retention. Recruitment activities will be monitored on a regular basis utilizing the Recruitment Tracking Form listed in the Manual of Procedures.

16.1.2. Study Monitoring Plan/Site Visits

A dedicated DCC Project Manager, reporting to Drs. Redline and Wang, will oversee the coordination of key activities across the DCC, CCC and field sites. S/he will oversee the development of the protocol, training materials, IRB templates and will coordinate a central training session that will be held at the beginning of the study. S/he will oversee the certification of staff on all procedures prior to their performance on study participants. S/he will conduct ongoing monitoring of site-specific activities and support each site's coordinator, including holding weekly to monthly conference calls that include Operations and Recruitment and Retention subcommittee calls. S/he will coordinate communications across study members and study entities using video conference calls (GoToMeeting) and ensure the web site is kept updated with appropriate study documents and reports. With the support provided by a web-portal and data reporting system developed by the DCC Informatics Core, s/he will monitor site and individual technician performance, share results with key study members (including the Steering Committee), and provide additional support to individual sites or study members as needed, including retraining or recommendations for remediation. Recruitment and retention benchmarks and data integrity will be closely monitored and if milestones are not met, the site PI and Steering Committee will be notified and procedures for remediation will be implemented. Formal site visits will occur as described below. Additional site visits will be scheduled if problems are identified or if subsequent performance problems occur. All Quality Assurance and Regulatory Compliance measures will be explicitly detailed in a Data and Safety Monitoring Plan specifically developed for this project. This plan will be filed with the NHLBI and study Data and Safety Monitoring Board (DSMB). This plan will identify the frequency and manner with which these activities will be conducted.

16.1.3. Site Visits

Within approximately 3 months of initiating data collection, each site will undergo a formal site visit by a team that will include members from the DCC and CCC. One member from an alternative clinical site may also participate. Site visits will generally last two days (including one night observing the polysomnography hook-up) and are designed to identify early in the study any departures from procedure, as well as to provide positive reinforcement to the staff and further improve the bonding among staff from across the study. Activities include; review of staff performance during a typical recruitment and data collection encounter, review of supply inventories, study documents, equipment cleaning procedures, and data audits. A formal site visit report is produced within one week of the visit, which is shared with the site, Steering Committee and DSMB. Additional site visits will be scheduled if problems are identified in the initial visit, or if subsequent performance problems are identified at the site.

16.1.4. Recruitment and Retention Monitoring

A Recruitment and Retention Subcommittee will be established with representation by the Study Coordinators from each clinical site, the DCC, one study otolaryngologist, and an investigator with experience in multicenter clinical trials. The committee will generate recruitment brochures, oversee the development of newsletters, nondenominational holiday cards and web sites targeting participants, and oversee the use of incentives (monetary and small gifts). Recruitment and retention statistics will be posted on a study web site monthly, along with graphs that show deviations from projections. Sites which fail to meet projections for 2 consecutive months will be asked to provide a report, with an analysis and action plan, to the Steering Committee. If continued lags are observed,

the study PIs (Furth; Redline), in consultation with the DSMB and NHLBI, will determine further actions, which may include replacement of the site or reallocation of funds.

16.1.5. Ongoing training

In addition to the initial central training, on-going training of project personnel will be conducted. This training, in the form of telephone conferences, is designed to maintain a current level of project knowledge regarding developments post initial training.

16.1.6. Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the DSMB/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. Clinical and Translational Science Award, Sleep Lab/Clinic, ENT clinic, diagnostic laboratory, and surgical suite, if appropriate).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

17. Data Safety and Monitoring Plan

The Data Safety and Monitoring Plan is outlined in the DCC application.

18. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects will be provided with a consent form describing the study and providing sufficient information to make an informed decision prior to entering. The consent form template may be modified slightly from site-to-site depending upon local IRB requirements and will be submitted with the protocol for review. Formal consent of a subject, using the IRB- approved consent form, must be obtained before that subject is submitted to any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

19. Statistical Analysis Plan

Description of study

We propose to conduct a randomized, single-blinded, controlled 12-month intervention study that evaluates the impact of early adenotonsillectomy [eAT] on measures of behavior, quality of life, and health care utilization (HCU) in children with mild sleep disordered breathing (MSDB). The study's co-primary outcomes are a well-validated and clinically informative measure of behavior associated with executive function (Behavioral Rating Inventory of Executive Function [BRIEF2/P] Global Composite Score [GEC]), assessing self-regulation and organizational skills, and an age-appropriate, validated measure of attentional vigilance, the Go-No-Go [GNG] continuous performance test (signal detection parameter, *d')*. Additional secondary outcomes will provide information relevant to patients, their caregivers, and the health care system. These include: other behavior measures, sleep disordered breathing (SDB) symptoms, generic and disease-specific measures of quality of life, indices of HCU, and polysomnographic indices of SDB and sleep quality. Analyses investigating effect modification by factors such as age, asthma, obesity, secondhand smoke exposure, sleep duration, and race will be conducted to explore subgroup variation in treatment response.

Children aged 3 to 12 years, with habitual snoring without frank obstructive sleep apnea (OSA), who meet study eligibility criteria, will be recruited from 5 well-established pediatric sleep centers, and further screened with polysomnography to exclude frank OSA and other sleep disorders. It is anticipated, based on the literature and our experience conducting similar screening in CHAT, that ~50% of participants will be eligible after screening PSG. 460 eligible participants will be randomized to either eAT or to watchful waiting with supportive care (WWSC) for 12 months. All participants will receive information about healthy sleep habits for children, and appropriate clinical referrals for management of co-morbidities such as asthma. Participants will undergo

standardized assessments including behavioral, performance, and health evaluations at baseline and at 6- and 12-month follow-up time points. Monthly check in visits will be conducted by telephone, email and/or text messaging to maintain participant contact and enthusiasm, and to collect additional symptom and health care utilization reports. Following 12 months, participants in the WWSC group will be referred to ENT for a clinical visit, if their 12-month PSG shows an AHI≥ 3 /hr or obstructive apnea index > 1/hr. or if the parent/caregiver reports concerns or symptoms. The 12-month end point was chosen to enable assessment of long-term therapeutic effects. However, data from the 6-month visit will be used to improve the study's statistical efficiency; help identify the time-course and trajectory of treatment response; and provide information for imputing missing 12-month data. In addition to the efficacy analyses described below, adverse events will be summarized and presented by treatment groups.

Aims, Hypotheses and Endpoints

Aim 1: To determine the effect of eAT on behavior, attention, SDB symptoms, sleep quality, and quality of life in children with MSDB.

Aim 2: To determine the effects of eAT on health care utilization (HCU) in children with MSDB.

Aim 3: To identify factors that moderate the response to AT, including age, asthma/atopy, obesity, secondhand smoke exposure, sleep duration, family functioning socioeconomic status, and race.

Endpoint for Primary Efficacy Hypotheses
The co-primary outcome of the randomized controlled trial will be the GEC Score from the BRIEF2/P and the GNG. Please see the CCC application for details on its reliability, responsiveness, and psychometric properties.

Primary Null Hypothesis
The primary null hypothesis is that the mean change at 12 months in the BRIEF2/P GEC Score and GNG sustained attention d' will be the same for children who were randomized to eAT or to WWSC.

Secondary Null Hypotheses
a) There will be no difference between treatment groups in the expected mean change at 12 months in other behavior/performance measures, SDB symptoms, and quality of life.

b) There will be no difference between groups in expected HCU (illness or injury requiring hospitalizations; emergency department visits; inpatient procedures; outpatient procedures; scheduled office visits; unscheduled office visits or urgent care visits; medication use) during the 12-month study period.

c) Any differences in outcomes (BRIEF2/P, GNG, HCU) between children randomized to eAT or to WWSC will not vary by age, baseline overweight/obesity, atopy/asthma status, secondhand smoke exposure, family and neighborhood socioeconomic status, family functioning, baseline symptom severity (i.e., Sleep Disordered Breathing Scale) or race (African American vs other; Minority vs. non-minority).

Exploratory Analyses
Analyses addressing secondary hypotheses will be considered exploratory. These include mediation and moderation analyses.

As snoring is the focus of this study, we will assess the association between quantitative estimates of snoring with study outcomes at baseline, evaluate the treatment effect on these snoring measurements, and whether changes in snoring correlates with changes in study outcomes, as an exploratory analysis.

Variables Used to Stratify Randomization

Randomization will be stratified by the following factors within site: age (≤ 5 years vs > 5 years); overweight status (body mass index [BMI] >85%ile); and race (African American vs other). These represent key groups likely to influence treatment responses. Stratification by these factors will provide greater assurance that the comparison groups will be similar with respect to these and related variables. Given an overall sample size of 460 and a relative large number of strata (8 strata within each of the 5 sites), we will use a dynamic randomization method, Pocock and Simon's minimization method[71], implemented in the Data Management System (Slice), to ensure treatment arms are balanced with respect to these factors as well as for the number of subjects in each group. Because the minimization method is more complex than stratified permuted blocks, Dr. Wang will monitor the randomization assignment closely to ensure the integrity of randomization.

Estimated Power and Sample Size

The study plans to randomize 460 subjects into one of the two arms in a 1:1 ratio. Based on the experience in the CHAT study, we assume a dropout rate of 15% at 6 months, and an additional 5% attrition at 12 months, resulting in 390 and 368 evaluable subjects at 6 and 12 months, respectively. As described below, this sample size was chosen so that the study will have ample power to detect moderate to large moderation effects and a range of mediation effects when the exposure-moderator and moderator-outcome associations are moderate or large.

The primary endpoints of the study are changes from baseline to 12 months in the BRIEF2 GEC score and the GNG d' score. The primary alternative hypotheses are that children randomized to the eAT group in comparison to WWSC will have a significant improvement in behavior as measured by the BRIEF2/P GEC score and GNG continuous performance d' score at the end of 12 months. To maintain a study-wise significance level of 5% for analysis of co-primary endpoints, the Holm method[72;73] will be used. The Holm method has been shown to be uniformly more powerful than the Bonferroni procedure. The Holm method is a sequentially rejective method for performing multiple tests. In the case of two tests using an overall alpha of 0.05, the comparison with the largest difference will be tested at the 0.05/2=0.025 level. If it is rejected, the comparison with the second difference will be tested at the 0.05 level.

We anticipate that 12-month changes in the BRIEF2/P GEC score in a sample of young children with MSDB will be comparable if not larger to that observed in the sample of children with OSA studied over 6 months in the CHAT study. In CHAT, the estimated

difference in change score from baseline to 6-month in the BRIEF GEC score in the eAT group compared to the WWSC group was 3.7 points. The standard deviation at baseline in the WWSC group was 11.5 and the correlation between the baseline and the follow-up GEC score was 0.73. For the GNG score, the anticipated treatment difference is 0.33, based on a published study that found a difference between 5-year-old with *vs* without SDB on an objective attention test[74]. In a study of 105 5-year old children studied with the GNG test at baseline and then 12 months later[75], Co-I Taylor observed the baseline GNG score to have a standard deviation of 0.77 and to correlate with the 12-month follow-up score with an r=0.48. Using these estimates and methods described in Hedeker *et al* for sample size estimation for longitudinal designs with attrition, our sample size with the assumed attrition rate has 98% power to detect a difference of 3.7 points in the BREIF2/P GEC change score and 98% power to detect a difference of 0.33 points in the GNG change score between treatment groups at a significance level of 2.5% and 5% respectively (the comparison for the BRIEF2/P GEC change score corresponds to a larger standardized effect and therefore is tested at a lower significance level of 0.025). The minimal effect size the study has 80% power to detect is 0.22 (0.24) for the GNG change score, and 2.4 (2.6) for the GEC change score at 5% (2.5%) significance level.

To detect the effect of eAT on health care utilization, in Aim 2 we will compare between group rates of hospital admissions, emergency department/unscheduled office visits, specialty consultations and medication use during the year following randomization. We estimate power based on the report by Tarasiuk *et al* who analyzed administrative health records in Israeli children with OSA[10]. Among children who underwent AT compared to those who did not, the number of new hospitalizations per child per year was 0.06 and 0.25, the number of emergency department visits per child per year was 0.35 and 0.37, and the number of specialist consultations per child per year was 1.9 and 3.5, for the treated and untreated groups, respectively. Assuming that the rates of these events in the eAT and the WWSC group are similar to those observed in the treated and untreated groups in Tarasiuk *et al*, our study will provide ample power to detect the differences in number of hospitalizations or the number of specialist consultations. Specifically, a sample size of 368 (184 in each group) provides >99% power to detect the difference between the two distributions of number of hospitalizations at the 5% significance level using a two-sided Wilcoxon rank-sum Test, based on 2000 Monte Carlo samples from the alternative distributions: Poisson(.06) and Poisson(.25). Similarly, our sample size provides >99% power to detect the difference between the two distributions of number of consultations at the 5% significance level using a two-sided Wilcoxon rank-sum test, based on 2000 Monte Carlo samples from the alternative distributions: Poisson(1.9) and Poisson(3.5). We will have limited power to detect differences in the patterns of emergency department visits if our emergency visits mirror those in the Israeli study. However, due to the high prevalence of asthma projected in our sample and the emergency room patterns in the U.S., we expect to see larger changes in this outcome.

Aim 3 is to identify factors that moderate the behavior and health care utilization changes in response to surgery (AT). As described in the CCC application, we anticipate that 50% of children will be age less than 5 years; 47% will be overweight/obese; 40% will be African American (AA), 30% will have asthma, and 20% will be exposed to secondhand smoke. The study will have 80% power to detect a treatment effect difference of 0.58, 0.59, 0.60, 0.64, and 0.74 standard deviations for interactions between treatment and age, overweight/obese, race, asthma, and secondhand smoke, respectively. In the CHAT study, the estimated difference in treatment effect on BRIEF

GEC score between AAs and non-AAs was 4.63 and the estimated standard deviations in the 4 subgroups defined by treatment and race ranged from 7.69 to 9.27. Assuming that the difference in treatment effect between AAs and non-AAs is 4.63 and a standard deviation of 9, a sample size of 184 per treatment group with 40% AAs provides 67% power to detect this difference (a 0.51 standard deviation of treatment effect difference) based on normal approximation at the 5% significance level.

Due to the considerable morbidity and HCU among children with asthma, it is of particular interest to assess changes in HCU with surgery within this group of children. National data demonstrate that asthma exacerbations occur in 57.2%, emergency room/unscheduled visits in 32.5%, and hospitalizations in 8% of children with asthma annually[75]. Further, we and others have shown that SDB is associated with severe or difficult to treat asthma[22,26,62,76]. SDB symptoms alone appear to predict asthma exacerbations as shown in the prior research[22,26,76] and a secondary analysis of data reported in Ross et al[26] which showed that 25% of children with habitual snoring had ≥ 3 asthma exacerbations over one year in contrast to 6.8% of those without snoring ($p<0.01$)[26]. Within our asthma subgroup, we will analyze an aggregate measure of HCU, "asthma exacerbations", defined according to NIH guidelines[77] as use of oral or systemic corticosteroids, unscheduled or emergency visits during which the child was treated with a short acting bronchodilator, or hospitalizations for asthma/wheezing. Using effect sizes observed in an uncontrolled study that reported that AT was associated with a reduction in asthma exacerbations from 4.1 ±1.3 per person per year to 1.8 ± 1.4 per person per year[62], we estimate that in our sample of children with asthma (110 evaluable 12-month endpoints), we will have >99% power to detect the difference between the two distributions of number of asthma exacerbations at the 5% significance level using a 2-sided Wilcoxon rank-sum test, based on 2000 Monte Carlo samples from the alternative distributions: Poisson(1.3) and Poisson(4.1). We have 80% power to detect a 27% reduction in exacerbation rate from a baseline rate of 4.1 per person per year.

The power to detect potential mediation effects (see below) depends on not only the mediation effect, but also on the magnitude of the association between exposure (X) and mediator (M) and the association between outcome (Y) and mediator controlling for exposure. As determined in simulation studies by Fritz and MacKinnon[76], a sample size of 368 achieves greater than 80% power to detect mediation effects ranging from small, to medium, to large (corresponding to a path coefficient of 0.14, 0.39 or 0.59) for the settings with moderate to large X-M and M-Y associations using various resampling methods including the PRODCLINC program[77], the percentile bootstrap, and bias-corrected bootstrap methods[78]. For the settings where one of the X-M and M-Y associations is small, a sample size of 368 achieves close to 80% power if the other association is moderate or large using the bias-corrected bootstrap method.

Approaches to the Analysis

Primary analyses will follow the "intention-to-treat" principle; that is, individuals will be analyzed according to their assigned treatment group, whether or not they receive the study treatment as assigned. This approach avoids bias if individuals drop out of the two arms for different reasons. Every effort will be made to obtain follow-up data on all children randomized, whether or not they follow their assigned treatment. Although every effort will be made to minimize missing data, some missing data will be inevitable, and therefore a variety of methods that accommodate missing data in analyses will be

considered, including inverse probability weighting and multiple imputation. For example, missing covariates may be imputed through the multiple imputation through chained equations (MICE) approach[79] and missing outcomes may be handled through the use of mixed effects modeling or inverse probability weighting[80 81]. We will make explicit the assumptions for the methods employed and perform sensitivity analyses to assess the robustness of results to plausible violations of these assumptions. Sensitivity analyses will be conducted excluding children on ADHD medications.

Preliminary Analyses

Our approach will involve close collaboration between clinical experts and biostatisticians while ensuring appropriate blinding. Interim analyses of baseline variables (aggregated across intervention groups) will be conducted early in the study to ensure that the collected and derived data follow the assumed distributions, and that appropriate methods for identifying outliers and for computing clinical scores are implemented. Reports will provide a full description of the distributions of each study variable, along with indices of associated data quality, and include graphic displays. The amount and patterns of missing data, if any, will be characterized. Measures that are not normally distributed may be transformed to meet model assumptions. In some instances, such as symptom summaries for related outcomes, outcomes may be derived by combining several variables into a small set. Before conducting final analyses, descriptive statistics will be generated using the total data set, ensuring that outliers or potential discrepancies in the data are resolved.

Descriptive Comparisons between Treatment Groups, Baseline and Over Time

Descriptive analyses will be performed to characterize the treatment groups, and to confirm that the randomization resulted in no important group differences at baseline. Summary statistics such as means, medians, standard deviations, and ranges also will be used to describe changes from baseline to Month 6, and from baseline to Month 12, for all primary and secondary outcome variables within each treatment group, as well as to describe dropout rates, treatment failures/cross-over rates, and patterns of missing data. Graphical methods such as stem-and-leaf diagrams, box plots, and scatter plots, will be used to examine distributions, and guide the choice of transformations. Two-group comparisons will generally employ Wilcoxon rank-sum tests to protect against violations of normality assumptions. Categorical variables, including dichotomous factors, will be summarized by proportions, and compared among groups using Fisher's exact test.

Statistical Approaches to Testing for Treatment Differences

To compare changes in the BRIEF2/P GEC score and GNG score at 6 and 12 months in the eAT and WWSC groups, we will perform a longitudinal analysis with time (0, 6, and 12 months) as a categorical variable, and with the assumption of equal means at baseline to reflect the randomized design. Both visit and treatment group will be treated as categorical variables to allow separate comparisons of intervention groups at 6 and 12 months. This analysis will also permit testing of the null hypothesis that the means of changes in BRIEF2/P scores and GNG scores at 6 and 12 months are the same in the eAT and WWSC groups. The model and testing procedure are:

*Let X1 and X2 be indicator variables for time = 6 months and time = 12 months, and let X3 be the indicator variable for treatment group. We will fit a mixed effects model for repeated measures that includes the main effects of X1 and X2, and the interactions between X3 and the two indicator variables for time, X1 and X2. Let β3 and β4 denote the coefficients of the interaction terms X1*X3 and X2*X3, respectively. β3 and β4 represent the treatment effects at 6 and 12 months and the average treatment effect is given by (β3 + β4)/2. Standard methods will be used to estimate and test the null primary hypothesis of β4 =0.*

Comparisons will be adjusted for stratification factors, and as appropriate, adjusted for potential covariates found to differ between groups at baseline and for baseline levels of other relevant covariates. Because the GnG test versions were developed for three broad age groups (with increasing difficult with higher age) we will address statistical adjustments that may be needed to accommodate heterogeneity in test difficulty across versions.

Secondary Analyses

Aim 1: We will use the Wilcox rank-sum test to compare group changes in secondary behavior/performance measures including the GNG inhibitory control d'-prime and the average of the sustained attention d-prime and inhibitory control d-prime, SDB symptoms and quality of life endpoints over the 12-month study period. Generalized linear regression models will be used to model treatment effects adjusting for covariates. All outcomes other than PSG indices will be available at 6 months and 12 months and thereby can be analyzed using the mixed effects model outlined for the primary analysis, which does not assume a linear trajectory over time. For continuous outcomes which appear to have a linear trajectory over time, we will also estimate the rate of change in each treatment group and test the null hypothesis that the rates of change are equal for the eAT group and the WWSC group using the following mixed effects model:

*Let T denote time and T=0, 1, 2 refer to baseline, month 6 and month 12. Let X3 denote the treatment indicator as before. The model will have each of the outcomes as response and include the main effects of T and the interaction effect of T*X3. The coefficient for T*X3 represents the treatment effect on linear trajectories.*

Standard methods can be used to estimate this effect and test the null hypothesis of a zero effect.

For PSG indices (e.g., metrics of overnight hypoxemia, hypercapnia, sleep architecture, and breathing patterns) that are only available at baseline and 12 months, similar models can be used except that the variables corresponding to 6 months will be removed from the model. All participants enrolling in PATS entered the trial with an apnea-hypopnea index (AHI) under 3, i.e., without any evidence of obstructive sleep apnea syndrome (OSA). Estimating the proportion of participants who went on to develop OSA during the trial is thus of particular interest. We will also evaluate treatment effects on the proportion of participants with emergence of OSA (as defined by an AHI ≥ 3) and 5 (indicating emergence of moderate or more severe OSA) at 12 months, and whether treatment effects differ by subgroups specified in Aim 3.

If we observe differences in behavior and vigilance between groups, we will determine whether improvements in vigilance explain a significant portion of the improvement in behavior, using the steps to establish mediation outlined by Baron and Kenny[84], which consist of fitting a series of regression models and testing relations among variable corresponding to significance tests of the regression coefficients. Specifically, we will construct regression models with change from baseline to 12 month BRIEF2/P GEC score as the outcome, including a treatment indicator as an independent variable, with and without including the change in the Go-No-Go performance test as a covariate. We will compare the coefficients for the treatment indicator to examine how much of treatment effect on the BRIEF2/P is explained by changes in the GNG test. Point and interval estimates for the reduction in the coefficients will be provided. Similarly, if sleep duration (by actigraphy and parent report) and sleep-quality (by PSG and parent report) demonstrate treatment effects, we will explore these factors as potential mediators for changes in behavior and vigilance (if these outcomes show treatment effects).

Aim 2: For endpoints related to HCU (illness or injury requiring hospitalizations; emergency department visits; inpatient procedures; outpatient procedures; scheduled office visits; unscheduled office visit or urgent care visits; medication use), incidence rate per person will be calculated. Recognizing that these count data are likely to be non-normal and skewed, we will use Wilcoxon rank-sum tests to compare study groups. To better model the underlying distribution of the count data and take into account potential data dispersion and possible preponderance of zeros, we will use goodness of fit statistics (e.g., AIC/BIC), likelihood ratio tests or the Vuong test[82] to choose among the zero-inflated negative binomial models, zero-inflated Poisson models or regular negative binomial models. The models that best fit the data will be used to model treatment effect adjusting for covariates. Incidence rate ratios comparing treatment groups will also be reported. We also will describe distributions of medication classes (e.g., antibiotics, nasal anti-inflammatory medications, asthma medications) and reasons for hospitalizations, etc. by group to identify reasons for HCU differences (e.g., infection; respiratory illness). Analyses will be performed both including and excluding events associated with the intervention (surgery and pre- and post-operative care, but not include the polysomnography).

Aim 3: Whether treatment effects pertain to some subgroups and not to others are of great clinical significance. Statistical tests of treatment by covariate interaction will be performed to assess whether treatment effect varies by age, baseline weight, atopy/asthma status, secondhand smoke, socioeconomic status, family functioning, baseline symptom severity (e.g., Sleep Disordered Breathing Scale) or race. Within the group of children with asthma, we will assess whether asthma exacerbations differ by treatment group, using similar approach for count data as described in the analysis for HCU indices.

If we identify race differences in treatment effects, we will explore whether those differences are explained by the measured social and environmental factors, such as measures of family functioning or secondhand smoke exposure. To address this question, we will use models similar to the mediated baseline by treatment interaction models proposed by Baron and Kenny[84] and MacKinnon[86], except that the mediators under consideration will be those measured social and environmental factors mentioned above. More specifically, we will fit the following models: (1) Y=i_1+ c_1X+c_2Z+c_3XZ+e_1; (2) Y=i_2+$c_1^{'}X$+ $c_2^{'}Z$ + $c_3^{'}XZ$ + bM + e_2; (3) M=i_3+ a_1X+a_2Z+a_3XZ+e_3, where Y denotes the outcome (e.g., BRIEF2/P GEC change score or GNG change score), X denotes the

treatment indicator, Z denotes race, and M denotes the potential mediator (measured social and environmental factor under consideration) for the racial differences in treatment effects (c_3). Our interest here is to explore the potential mediation effects corresponding to the effect of XZ to M to Y, through evaluating the significance tests for $\widehat{c_3}$, $\widehat{a_3}$, $\hat{b}$, and $\widehat{c_3'}$ (or $\widehat{a_3}\hat{b}$), the estimates of corresponding regression coefficients.

One gap in the CHAT study was lack of objective data on nightly sleep duration, which may significantly influence behavior and cognition. In this study, we will evaluate whether baseline average nightly sleep duration and continuity obtained from in-home actigraphy are associated with: a) baseline behavior and performance measures; b) whether there is an interaction between sleep duration and treatment. Models will be similar to those described above. We also will evaluate whether changes in sleep duration and continuity are associated with changes in behavior and performance outcomes.

Impact of Coronavirus Disease 2019 (COVID-19) Pandemic

We will summarize data quality and missingness by whether the relevant visit (at baseline, 6 months, or 12 months) occurred (or was scheduled to occur) prior to or following 03/11/2020, the date on which the World Health Organization declared COVID-19 to be a global pandemic.

As a sensitivity analysis, we will examine the robustness of the co-primary efficacy analyses to the mid-trial onset of the COVID-19 pandemic. To do so, we will incorporate an indicator of pandemic onset as an additional covariate and consider its interaction with the visit and treatment group by visit interaction factors. Specifically:

Let B_{ij} be the jth recorded BRIEF GEC score for the i^{th} participant, let $X1$ and $X2$ be indicators of the 6-month and 12-month visit, respectively, and let $X3_i$ be an indicator of randomization to the eAT arm. Let C_{ij} be an indicator of whether the jth measurement for the ith participant was recorded following the onset of the COVID-19 pandemic (dated on 03/11/2020). We will fit the model

$$B_{ij} = \beta_0 + \beta_1 X1_{ij} + \beta_2 X2_{ij} + \beta_3 X1_{ij} * X3_i + \beta_4 X2_{ij} * X3_i + \beta_5 C_{ij} + \beta_6 X1_{ij} * C_{ij} + \beta_7 X2_{ij} * C_{ij} + \beta_8 X1_{ij} * X3_i * C_{ij} + \beta_9 X2_{ij} * X3_i * C_{ij} + b_i + \epsilon_{ij}$$

from which we will calculate the estimated mean baseline BRIEF GEC scores (or GNG sustained attention d' measures), as well as the changes in those scores from baseline to 6 months and from baseline to 12 months in each randomization arm, both before and during the COVID-19 pandemic:

- Estimated mean baseline score pre-pandemic: $\hat{\beta}_0$
- Estimated mean baseline score during the pandemic: $\hat{\beta}_0 + \hat{\beta}_5$
- Estimated mean change at 6 months (WWSC arm) pre-pandemic: $\hat{\beta}_1$
- Estimated mean change at 6 months (WWSC arm) during the pandemic: $\hat{\beta}_1 + \hat{\beta}_6$
- Estimated mean change at 12 months (WWSC arm) pre-pandemic: $\hat{\beta}_2$
- Estimated mean change at 12 months (WWSC arm) during the pandemic: $\hat{\beta}_2 + \hat{\beta}_7$
- Estimated mean change at 6 months (eAT arm) pre-pandemic: $\hat{\beta}_1 + \hat{\beta}_3$

- Estimated mean change at 6 months (eAT arm) during the pandemic: $(\hat{\beta}_1 + \hat{\beta}_6) + (\hat{\beta}_3 + \hat{\beta}_8)$
- Estimated mean change at 12 months (eAT arm) pre-pandemic: $\hat{\beta}_2 + \hat{\beta}_4$
- Estimated mean change at 12 months (eAT arm) during the pandemic: $(\hat{\beta}_2 + \hat{\beta}_7) + (\hat{\beta}_4 + \hat{\beta}_9)$

We will then assess the pandemic's impact on the randomized treatment effects by using standard methods to test the null hypothesis of $\beta_9 = 0$, and will assess its impact on children's BRIEF global composite scores (or GNG sustained attention d' measures) overall by testing the null hypothesis of $\beta_5 = \beta_6 = \beta_7 = \beta_8 = \beta_9 = 0$.

Data Quality Monitoring and Interim Monitoring

The study will be monitored routinely for issues of data quality, study conduct (including recruitment and follow-up rates), data quality and adverse events. Of particular concern will be attrition and cross-over rates which, if excessive, could jeopardize the integrity of the study. Monthly reports addressing these issues of study conduct, data quality and adverse events will be provided to the Steering Committee (aggregate data), and periodically to the DSMB and NIH. Given that the patient population consists of children who are otherwise healthy, who have mild SDB, and that the intervention is considered a standard clinical intervention, we do not anticipate that the interim analysis will yield efficacy data compelling enough to require early termination. However, we will propose to monitor the BRIEF2/P GEC score and GNG score, our primary outcomes, in planned interim analyses of efficacy and safety. We plan to perform one interim analysis after half of the study population has completed their 12-month evaluations. Based on our recruitment projections, most of the accrual will be complete at this time and therefore early stopping may not be relevant. To create a formal framework for assessment of interim results, the Haybittle-Peto boundary[85] will be used. That is, interim results for comparisons of the BRIEF2/P score and GNG score between treatment groups will be considered sufficient to consider early termination only if at least one of the between-group differences are statistically significant using a family-wide significance level of 0.001. The Haybittle-Peto stopping rule allows the final analysis to be evaluated at a 5% level of significance[85;86]. Concurrence with the monitoring plan by the PI's, the DSMB and the NIH will be required prior to implementation of the plan.

Interim comparative data will be considered confidential and will be available only to the DSMB members and to the DCC statistician analyzing the interim data and preparing the DSMB report.

Statistical Software

The software of choice for most of the analyses will be SAS 9.4, which has a wide range of statistical methods, and provides the routines for the multiple linear regression as well all other statistical methods planned for this trial. Where necessary, SAS may be supplemented with procedures from other software packages such as STATA or R.

APPENDIX A: PATS VISIT SCHEDULE

	Preliminary Screen		Confirm Final Eligibility	**eAT Only**	Visits for Both Arms				**WWSC Only**
Procedures and Assessments	ENT **V1**	PSG **V2**	Baseline **V3 Randomize V4**[7]	**Surgery V5**	Phone[12]	Interim **V6**	PSG **V7**	Endpoint **V 8**	**ENT Re-eval**
Visit	**Screen**		**Baseline Day 0**	**eAT Only**	**Phone**	**Clinic**	**PSG**	**Clinic**	**WWSC Only**
Time	Day -60 to -1		At baseline or within 48 hrs of baseline	M1 W/in 1-4 wk randomized	,M2, M4 ,M8, M10,	M6	M12	M12	1-4 wks after M12
Preliminary eligibility review; informed consent[1]	**X**	**X**							
ENT evaluation[2]	**X**								
PSG[3]		**X**					**X**		
Randomize			**X**						
Surgery				**X**					
Re-evaluation for surgery (**WWSC only**)								**WWSC** Remind family	**X If indicated**
Urine cotinine[4]			**x**						
Resting BP			**X**			**X**		**X**	
Anthropometry			**X**			**X**		**X**	
Physical exam			**x**						
Behavioral performance testing[5]			**X**			**X**		**X**	
Parent questionnaires[6]			**X**			**X**		**X**	
Serum IgE[4]			**X**						
Healthy sleep education [8]			**X**						
Sleep Diary			**X**			**X**		**X**	
Behavioral rating scales: teacher[10]			**X**			**X**		**X**	
Adverse event, medication, and HCU inquiry[11]		**X**	**X**		**X**	**X**		**X**	

NOTES

1. Preliminary screening/ascertainment of eligibility and the face-to-face consent discussion will occur at slightly different points of participant interaction, depending on the local site's recruitment strategies (sources: ENT, sleep laboratory, other clinics)
2. Existing ENT evaluations (within 90 days prior to randomization) can be utilized to establish primary eligibility for adenotonsillectomy surgical candidacy. WWSC group will be re-evaluated for surgery after month 12 (within 1-4 weeks of the month 12 visits).
3. An overnight PSG must be performed (with 60 days) and approved by the study's reading center prior to randomization. Another PSG is completed at the month 12 endpoint visits for those who are eligible and enrolled in the study.
4. Samples will be processed and stored locally for shipment to the CCC central repository monthly.
5. Child completes 2 behavioral performance tests (coordination, vigilance).
6. Parent completes behavioral rating scales and other questionnaires.
7. Not an actual visit. Listed in the database as Visit 4 for tracking purposes. Randomization is an administrative process that can easily be completed at the end of the baseline visit before the family leave the clinic (ideal).
8. Health sleep habits guidance Actigraph device initialized, verbal and written instructions provided at the baseline, interim, and endpoint visits to be returned in a pre-paid mailer after 1 week of recording at home.
9. Teacher completes 3 behavioral rating scales (BRIEF2/P, Conners, CBCL-TRF) at 3 time points: baseline, month 6 and month 12. Forms are sent (mailed by study staff) immediately after the visit.
10. Adverse event, medication, health care utilization (HCU) inquiries occur at all participant visits (verbally for phone visit; face-to-face for other visit types).
11. Monthly contact by telephone, email and/or text messaging at Months 1,2,3, 4,5,7,8,9, 10,11

APPENDIX B: PROJECT TIMETABLE

	Yr. 1				Yr. 2				Yr. 3				Yr. 4				Yr. 5			
	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Finalize Protocol																				
Local sites IRB Approval																				
Central Training; Certification																				
Pilot Studies																				
Enrollment																				
6 Month Follow Up Visits																				
12-Month Follow-Up Visits																				
DSMB Meetings																				
Interim Analyses /Data Query Resolution																				
Lock Data Base																				
Primary MS																				
Secondary MS (baseline data, etc)																				
Deposit In BioLinnc																				
Deposit in NSRR																				

APPENDIX C: ROSTER OF DSMB MEMBERS

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