

Protocol: A Randomized Controlled Study of Adenotonsillectomy for Childhood Sleep Apnea (CHAT)

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List of Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
AHI	Apnea Hypopnea Index
AT	Adenotonsillectomy
BMI	Body Mass Index
BP	Blood Pressure
CPAP	Continuous Positive Airway Pressure
CRCU	Clinical Research Computing Unit
CRF	Case Report Form
CRP	C-reactive Protein
CVD	Cardiovascular Disease
DCC	Data Coordinating Center
DMS	Data Management System
EAT	Early Adenotonsillectomy
ENT	Ears, Nose and Throat
HOMA	Homeostasis Model Assessment
HRQOL	Health Related Quality of Life
HTN	Hypertension
IMM	Independent Medical Monitor
LCBR	Laboratory for Clinical Biochemistry Research
MOP	Manual of Procedures
NHLBI	National Heart, Lung, Blood Institute
NP	Neuropsychological
NPQA	Neuropsychological Quality Assurance
OAI	Obstructive Apnea Index
OSAS	Obstructive Sleep Apnea Syndrome
PTF	Potential Treatment Failures
PSG	Polysomnography
QCC	Quality Control Center
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SCC	Scientific Coordinating Center
SQCC	Surgical Quality Control Core
SWS	Slow Wave Sleep
URMF	Urgent Referral Medical Form
UMRC	Urgent Medical Referral Criteria
URA	Urgent Referral Alert
WWSC	Watchful Waiting with Supportive Care

Study Summary

Title	A Randomized Controlled Study of Adenotonsillectomy (AT) for Childhood Sleep Apnea
Short Title	CHAT
Special Population	Children (male and female) Ages 5.0 – 9.99 years of age
Methodology	Parallel, randomized, single-blind, multicenter design
Study Duration	5 years
Clinical Study Center(s)	Multicenter study
Objectives	<ol style="list-style-type: none"> 1. To assess the effect of early AT (EAT) surgery versus Watchful Waiting with Supportive Care (WWSC) in children with Obstructive Sleep Apnea Syndrome (OSAS). 2. To determine improvements in neurocognitive functioning (executive attention domain) between the two arms at the end of 7 month period of observation. 3. To assess the extent to which AT improves breathing disturbances and sleep quality in children with OSA. 4. To assess whether the effects of AT differ according to race and/or weight category 5. To assess the effect of AT in children with OSAS with respect to behavior, other indices of neurocognitive functioning (learning and memory, information processing, etc.), physical growth, blood pressure, metabolic profile, and overall quality of life. 6. To evaluate the relationship of changes in breathing disturbances and sleep quality to changes in neurocognitive functioning. 7. To assess the relationship of changes in breathing disturbances and sleep quality to behavior, other indices of neurocognitive functioning, physical growth, blood pressure, metabolic profile and overall quality of life.
Number of Subjects	460
Diagnosis and Main Inclusion Criteria	Obstructive apnea index OAI ≥ 1 or Apnea Hypopnea Index (AHI) ≥ 2 , confirmed on nocturnal, laboratory-based PSG, parental report of habitual snoring (on average occurring >3 nights per week), tonsillar hypertrophy ≥ 1 , deemed to be a surgical candidate for AT by ENT evaluation.
Study Intervention	Early Adenotonsillectomy (EAT)
Reference Intervention	Watchful Waiting with Supportive Care (WWSC)
Duration of Follow-up	7 Months
Statistical Methodology	The primary analysis comparing the change in the attention executive functioning score between the EAT and WWSC groups will be performed using Analysis of Covariance (ANCOVA) adjusting for the stratification factors of race, weight status, and site. Change will be defined as the difference between the 7 month and baseline responses. Secondary analyses of the primary outcome will rely on linear regression to evaluate whether observed differences, if any, are attributable to imbalances in prognostic factors such as baseline AHI as well as to the change in indices of OSAS that occurred during the intervention period. Additional analyses will be performed adjusting for other potential confounding variables such as gender and baseline values of BMI, neck size, and season of study entry and cognitive, behavioral and laboratory indices, but these will be subsidiary to the primary comparison. Standard regression diagnostics will be used to assess model adequacy, and to examine potential outlying or influential data points.

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1. Introduction

Pediatric Obstructive Sleep Apnea Syndrome (OSAS) is a common health problem, affecting 2-3% of children, with rates two to four-fold higher in vulnerable populations such as African Americans. Untreated, pediatric OSAS is associated with a wide range of adverse health outcomes, which may lead to chronic health sequelae.

Adenotonsillectomy (AT) is generally considered the first line treatment for childhood OSAS. This is the second most commonly performed pediatric surgical procedure, with OSAS the most frequent indication in academic medical centers. Nonetheless, there has not been a single randomized controlled study that has addressed the efficacy of AT. Although uncontrolled, short-term follow-up studies indicate that AT is often effective, other data indicate that residual OSAS may occur in certain subgroups, such as minority children, and in children with other OSAS risk factors, such as obesity. A rigorous controlled study with a sufficient representation of ethnic minorities and comprehensive follow-up is needed to address the role of this treatment in pediatric OSAS, and the potential differential effectiveness among obese children and ethnic minorities. We therefore have assembled a group of expert centers in pediatric OSAS to address the hypothesis that surgical treatment (AT) of OSAS in children aged 5 to 9 years will result in measurable improvements in health outcomes measured 6 months following AT. Children eligible for AT in standard practice will be randomized to expedited (early) adenotonsillectomy (EAT) versus Watchful Waiting with Supportive Care (WWSC) with surgical treatment decisions deferred until after a seven (7) month observation period, with continued follow-up through twelve (12) months.

2. Background and Rationale

2.1 High Prevalence of OSAS

Although adenotonsillar enlargement is the most commonly recognized risk factor for OSAS in children, the expression of the disorder, as well as response to therapy, may be strongly associated with other risk factors, such as obesity. The increased prevalence of childhood obesity over the last decade may be expected to result in a concomitant rise in OSAS, which may further increase disease burden in populations also at risk for obesity, such as ethnic minorities.

2.2 OSAS Morbidity Overview

OSAS is characterized by repetitive episodes of upper airway obstruction during sleep, often causing intermittent hypoxemia and hypercapnia, and sleep disruption. Other OSAS physiological perturbations include chemoreflex activation, increased central nervous system arousal, and sleep fragmentation with selective reduction of rapid eye movement (REM) and slow wave sleep (SWS). These physiological perturbations, when untreated, are thought to contribute to a wide range of adverse health outcomes. In children, the chronic health co-morbidities associated with untreated OSAS include cognitive deficits, behavioral problems (inattention, hyperactivity, aggression, conduct problems, Attention-Deficit/Hyperactivity Disorder (ADHD)), mood impairments, excessive daytime sleepiness, impaired school performance, and poor quality of life. Data from uncontrolled studies indicate that treatment of childhood OSAS with AT may result in improvements in learning, aggression, and hyperactivity, suggesting that such deficits may be reversible. Untreated pediatric OSAS also has been associated with adverse cardiovascular disease (CVD) and metabolic outcomes. Children with OSAS have higher levels of blood pressure, C-reactive protein (an inflammatory risk factor for CVD) and increased insulin resistance, as well as left ventricular hypertrophy, suggesting that childhood OSAS also may increase the risk of developing severe

chronic cardiovascular and metabolic conditions. OSAS also has been associated with failure to thrive in young children. Despite the frequency and severity of OSAS during childhood, there are large knowledge gaps, including scant data that address causal pathways and population vulnerability to the disorder. The overall efficacy of treatment in reversing sleep and breathing disturbances across pediatric subgroups is unknown, and the effect of treatment on morbidity is poorly understood. Since OSAS in children may differ from the adult condition in its etiology, clinical manifestations, and treatment, studies from adults cannot be extrapolated to children, and childhood OSAS needs to be studied in its own right. This study will be the first randomized, controlled study of the effects of surgical treatment (AT) on OSAS in children, including a systematic assessment of outcomes.

2.3 Neurological (NP) and Behavior Effects

A major component of OSAS morbidity relates to short, and possible, long-term NP deficits caused by exposure to intermittent hypoxemia, arousal, and sleep deprivation, acting independently or synergistically. Animal experiments have shown that intermittent hypoxemia, simulating exposures typical of OSAS, produces apoptosis in the cerebral cortex and hippocampus. These histological changes correspond to spatial learning deficits in animals. In adults with OSAS, imaging techniques have shown a range of cerebral abnormalities, some of which improved with CPAP treatment in uncontrolled studies. Preliminary work in children with OSAS and carefully matched controls using magnetic imaging spectroscopy also indicate cerebral metabolic differences in children with OSAS and controls, with increased choline/NAA levels, a marker of cerebral apoptosis and demyelination. Such imaging techniques, however, cannot be used feasibly in large pediatric samples (due to expense, procedural difficulties) and do not provide information on clinically relevant impairments. Therefore, in clinical studies, NP deficits have been examined using test batteries that assess a range of functions (broadly considered to assess different structural areas of the brain). Executive functions (planning, initiation, or self-regulation of goal-oriented behavior) are of interest since they are particularly dependent on the basal ganglia and frontal lobes, areas sensitive to intermittent hypoxemia.

2.4 Quality of Life

Measurement of health-related quality of life (HRQOL), a comprehensive and multidimensional construct, allows assessment of the impact of OSAS and its treatment on the child's daily activities, physical symptoms, social interactions, and emotional well-being. Such measures can help parents and providers weigh the risks and benefits of treating OSAS, inform decisions regarding treatment effectiveness, and support the rationale for diagnosis and treatment among third party payers. There is growing evidence that HRQOL is reduced in children with OSAS and that these measures are responsive to AT in the short and long term, supporting our hypothesis that treatment of OSAS by AT will be associated with improved HRQOL as measured by both generic and disease-specific measures.

2.5 Growth

Poor growth is a complication of childhood OSAS, possibly because of increased work of breathing during sleep, and abnormal nocturnal growth hormone secretion. Early reports cited a prevalence of failure to thrive of 27-56%. Although overt failure to thrive may be less frequent now because of a greater awareness of OSAS among pediatricians, children with OSAS often grow poorly, and have catch-up growth following AT. Even children in the normal range can have increased growth postoperatively. In a small study, z-scores for weight increased from -0.30 ± 1.47 to 0.4

± 1.34 within $10 \pm$ weeks after AT in 14 children with OSAS, ages 2 to 6. It is unclear what the effect of AT is on growth in obese children, although one study showed that obese children also gained weight postoperatively. In this study, we will examine the effects of AT on growth in children with OSAS. We predict that weight and height Z scores will significantly increase in children with OSAS following AT; we also will examine changes in overweight.

2.6 Pathogenesis of Childhood OSAS

Most childhood cases of OSAS are associated with adenotonsillar hypertrophy. Accordingly, standard of practice is to use AT as a “first-line” therapy. This is supported by uncontrolled studies showing that OSAS improves in approximately 70-80% of children after AT. Other support is derived from imaging studies showing that the volume of the upper airway is smaller, and the adenoid and tonsils are larger, in children with OSAS compared to controls. However, although the degree of obstructive apnea correlates with the size of the tonsils and adenoids, the correlation coefficient for this relationship is only 0.51, with considerable overlap in adenotonsillar size between children with OSAS and asymptomatic children, suggesting that factors other than adenotonsillar size may contribute to the pathogenesis of OSAS.

2.7 Need to Evaluate Treatment Efficacy

Standard of practice is to use AT as the primary treatment modality for childhood OSAS. Although the overall frequency of this procedure has diminished during the past 40 years, AT remains the second most common surgical procedure in children (5/1000 children/per yr; >248,000 surgeries/per yr). The proportion of these procedures performed specifically for OSAS has grown rapidly. A recent survey of nearly 200 otolaryngologists estimated that among 24,000 procedures performed in children aged 5 to 12 years, a bedside diagnosis of OSAS and recurrent tonsillitis were each major indications in about 40% of the cases, and the proportion with tonsillitis as an indication was much lower among surgeons in academic practice settings, subspecialty training in pediatric otolaryngology, or large practice volumes. The popularity of AT is in part based on data indicating that more conservative surgical procedures, such as adenoidectomy alone, are associated with poorer outcomes. Although alternative OSAS treatments, such as continuous positive airway pressure, can be administered successfully in children, this therapy is generally reserved for children who have failed AT or have clearly recognized risk factors other than adenotonsillar hypertrophy (such as specific craniofacial syndromes).

Despite the high frequency of AT and its use as first-line treatment for pediatric OSAS, information on its effectiveness is limited in both quantity and study design. Even more limited data address co-morbidities of OSAS following surgery. Taken together, the literature supports use of AT to improve PSG measures of OSAS as well as its major co-morbidities (subjective sleep quality, behavior, and quality of life). However, the existing research has serious methodological limitations, and, as with many other medical procedures widely practiced before effectiveness was adequately tested, the beneficial effects of AT in pediatric OSAS have not yet been proven. Prior studies have mostly been clinical series, many have been retrospective, others have not had optimal control or comparison subjects, and few have used well-validated measures of behavior, cognition, vascular function, or quality of life thought to be the main areas of vulnerability in OSAS. Most studies have relied on parent report of symptoms, with little to no objective measurement of cognitive functioning or independent appraisal of the child's behavioral functioning in the classroom. Under such circumstances, the potential for bias is high and the generalizability of findings across settings is questionable. Most

importantly, not one study has used a randomized controlled design, obscuring the degree to which outcomes, such as neurobehavioral improvements, perhaps the area of most concern to the families of OSAS children, may be truly attributable to treatment, rather than other factors (e.g., practice effects), or to natural variation in outcomes. Indeed, a recent Cochrane review indicated that, although AT is considered standard of practice for childhood OSAS, there was inadequate evidence supporting AT for childhood OSAS, underscoring the need for a rigorous controlled treatment study. Also, despite suggestions that some subgroups of patients may have inadequate response to AT, no study has assembled a sample size sufficiently large to determine whether AHI improves more in some subgroups than others. Furthermore, in the absence of any randomized, controlled treatment trial, fundamental knowledge about the pathophysiology of OSAS and its consequences remains limited. Proof that OSAS resolves with AT, and that OSAS co-morbidities such as hyperactive behavior are in fact OSAS consequences, can only be addressed with a randomized controlled treatment trial. Indeed, in light of other data that suggest that academic underperformance can persist years after the resolution of OSAS symptoms, it is imperative that the field gain a more scientifically-grounded understanding of the reversibility of OSAS-associated neurobehavioral deficits following AT.

2.8 Societal Costs Related to Childhood OSAS and its Surgical Treatment

The research has enormous health economic implications. Given a prevalence of childhood OSAS of 2%, >1 million US children aged <15 years are estimated to be affected. Annually, 248,000 procedures are performed, with an estimated half billion dollars in annual expenditures. Surgical rates vary across and within geographic regions by 36%. Variation in procedures is likely to be partially attributable to the paucity of an evidence base to guide management, underscoring the need for data that address the efficacy of AT. In addition to the costs of AT, failure to appropriately treat childhood OSAS may increase costs for acute health care. The economic and societal costs associated with inadequately treated OSAS could be magnitudes higher if OSAS plays a causal role in the development chronic neurobehavioral and cardiovascular disorders.

2.9 Summary

In summary, this study will fill a crucial gap in the literature and help guide more effective screening and intervention studies. Inclusion of sufficient ethnic minorities is of marked importance given potential susceptibilities of vulnerable groups from low socioeconomic status to multiple risk factors that may reduce academic performance and increase vulnerability to chronic CVD and metabolic diseases. Clinical trials are needed to assess the role of AT, given the millions of dollars of health care dollars spent on this procedure and the lack of data on long term effectiveness. This study will help identify which children are most likely to benefit from AT, which need long term follow-up, and which may benefit from alternative treatments or additional health recommendations. The timeliness of the study is underscored by the current childhood obesity epidemic. Obesity prevalence has tripled in the last decade and is likely to increase the prevalence of OSAS and may reduce the efficacy of AT. Overall, the data obtained could have critical implications for many thousands of children who undergo AT in the U.S. each year and others in whom AT should be considered.

The study will provide data that for the first time will address the role of AT and define the subgroups most suitable for this procedure. This study will be the first rigorously controlled and sufficiently powered study that will: a) systematically address clinically important outcomes in childhood OSAS; b) utilize a randomized controlled design; c)

address a wide spectrum of OSAS; d) utilize objective and highly standardized exposure and outcome measurements; e) include a racially diverse sample, with representation of overweight and non-overweight children.

3. Study Objectives

3.1 Primary Objective

To assess the effect of early AT (EAT) surgery versus Watchful Waiting with Supportive Care (WWSC) in children with OSAS with respect to neurocognitive functioning, specifically executive/attention functions.

3.2 Secondary Objectives

- To assess the extent to which AT improves breathing disturbances and sleep quality in children with OSAS.
- To assess whether the effects of AT differ according to race and/or weight category
- To assess the effect of AT in children with OSAS with respect to behavior, physical growth, blood pressure, metabolic profile, and overall quality of life.
- To evaluate the relationship of changes in breathing disturbances and sleep quality to changes in neurocognitive functioning.
- To assess the relationship of changes in breathing disturbances and sleep quality to behavior, physical growth, blood pressure, metabolic profile and overall quality of life.

4. Study Design

4.1 General Design

The study is a 7month, parallel, randomized, single-blind, multicenter study that compares early adenotonsillectomy (EAT) to Watchful Waiting with Supportive Care (WWSC) in children ages 5.0-9.99 years of age with documented Obstructive Sleep Apnea Syndrome (OSAS). The study is designed to compare the frequency of sleep-related breathing disturbances (apnea, hypopnea); neurocognitive function, including attention, executive functions, and learning and memory; behavior and mood; growth, blood pressure, including systolic, diastolic and pulse pressure; metabolic profile, including fasting insulin and C-Reactive Protein (CRP) levels; and quality of life, including physical and social functioning.

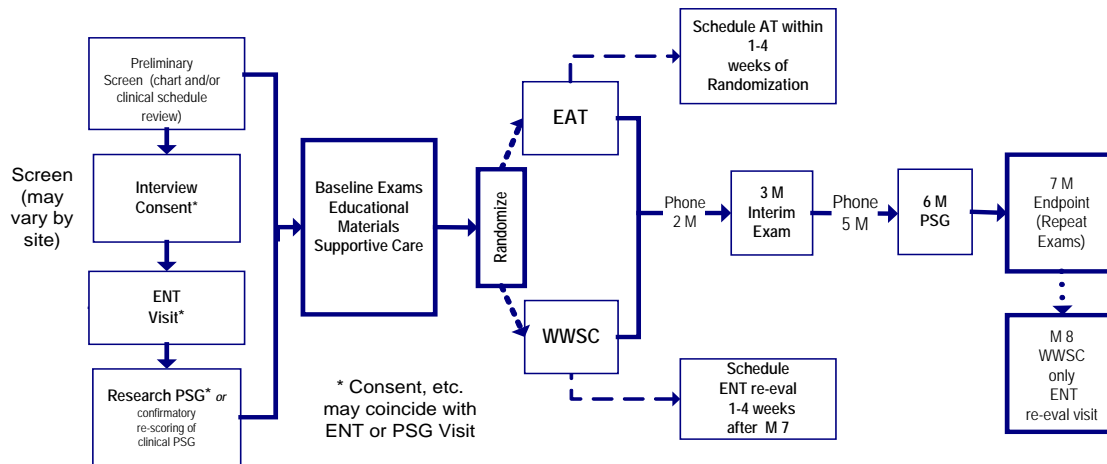
All participants who meet eligibility criteria at screening will be randomized to one of the following two treatment groups:

Early Adenotonsillectomy (EAT) performed by participating ENT surgeons, with treatment or referral for treatment of co-morbidities (e.g., asthma, allergic rhinitis), education regarding general sleep hygiene and healthy behaviors, and use of nasal saline spray as needed for nasal mucosal crusting or dryness.

Watchful Waiting with Supportive Care (WWSC), with treatment or referral for treatment of co-morbidities (e.g., asthma, allergic rhinitis), education regarding general sleep hygiene and healthy behaviors, and use of nasal saline spray as needed for nasal mucosal crusting or dryness, with re-evaluation by ENT and a decision to proceed with AT deferred until after the 7 month observational period.

Approximately 460 eligible children, 230 per treatment arm, will be randomized to EAT or WWSC, and followed for a period of 7 months..

4.1.1 Study Schema



4.2 Overview of Study Design

4.2.1 Screening and Baseline Visits

Screen ENT and sleep clinic referrals (chart and existing PSG review) to identify potentially eligible patients; contact referring physicians to ascertain study eligibility and assure HIPAA requirements are met.

- Obtain informed consent and confirm further eligibility criteria with parent interview (at clinic encounter or by telephone).
- Refer for ENT evaluation (if not done within 3 months of randomization) to confirm surgical candidacy.
- Perform research baseline PSG with central scoring, or perform central scoring of standardized clinical PSG and confirm final eligibility criteria
- Perform Baseline Assessments: Morning assessment visit with standardized assessments of anthropometry, neurocognitive and behavioral functions, general health and functional status, metabolic profile, and morning blood pressure (BP). Confirm final eligibility.
- Randomize to EAT *versus* WWSC

4.2.2 Follow-up Contacts

- 1 Month – **EAT arm only**: AT surgery Month 1 (1-4 weeks from randomization)
- 2 Month phone contact will be made for safety and adverse event monitoring and to reinforce general study participation.
- 3 month interim visit for safety and adverse event monitoring; BP, weight, height and to reinforce general study participation.
- 5 month phone contact will be made for safety and adverse event monitoring and to reinforce general study participation.
- 6 month research PSG will be conducted.

- 7 month primary outcome assessments: neurocognitive/behavioral functions, general health and functional status, metabolic profile, morning BP and anthropometry.
- 8 month - **WWSC arm only**: ENT re-evaluation (within 1-4 weeks of month 7 visit)

4.3 Study Organizations

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

- 1) Cincinnati Children's Hospital, Cincinnati, OH
- 2) Children's Hospital of Philadelphia, Philadelphia, PA
- 3) Rainbow Babies and Children's Hospital, Cleveland, OH
- 4) Cardinal Glennon Children's Hospital, St. Louis, MO
- 5) Montefiore Children's Hospital, New York, NY
- 6) Children's Hospital of Boston, Boston, MA

Additional clinical sites will be added as recommended by the Steering Committee and approved by the NHLBI. All new sites must have IRB approval and training on CHAT-specific procedures prior to site initiation and enrollment of participants.

In addition to the clinical sites, the organization includes:

- Scientific Coordinating Center (SCC) located at Harvard University, Boston MA, will provide scientific oversight of protocol development and assist with statistical analyses.
- Polysomnography Reading Center (SRC) located at Brigham and Women's Hospital a division of Harvard Medical School, Boston MA will provide central scoring of Polysomnography (PSG), confirm PSG eligibility and provide standardized PSG training and monitoring.
- Quality Control Center (QCC) located at the University of Michigan, Ann Arbor, MI, is comprised of two entities which will provide standardized data collection, testing methods and quality control for:
 - Neuropsychology Quality Assurance (NPQA) for data collected from neurocognitive and behavioral testing.
 - Surgery Quality Control Core (SQCC) for all data collected related to AT.

The QCC (NPQA and SQCC) will also oversee training and certification of psychometricians and ENT surgeons, when applicable.

- Laboratory for Clinical Biochemistry Research (LCRB) located at the University of Vermont, Burlington, VT, will serve as the central repository, providing storage of blood samples and laboratory analysis.
- Data Coordinating Center (DCC) located at the University of Pennsylvania School of Medicine, Philadelphia, PA. The DCC will provide data management/computing and biostatistical leadership and oversight for the design/conduct of the trial. Additional responsibilities include: 1) the preparation and distribution of study protocol and manual(s) of procedures, 2) collaboration

with study investigators in the development, testing, and use of all CRFs and study procedures, 3) database development and maintenance, 4) development of comprehensive data management plan and application of data quality assurance procedures, 5) coordination of training of study personnel, 6) site monitoring, 7) coordination and management of activities between technical and scientific teams and other organizational bodies associated with the study 8) communication with the DSMB through a web portal and/or protected section of the data management system providing members with access to project reports, documentation and adverse event summaries.

5. Study Endpoints

5.1 Primary Endpoint

The primary measure of functional improvement used to test the primary study hypothesis will be the Attention/Executive (A/E) Functioning Domain Index of the Developmental Neuropsychological Assessment (NEPSY), with the goals of 1) identifying whether this measure differs in each treatment group; and 2) whether improvement in score is associated with improved OSAS (i.e. reduction in AHI). The primary endpoint measure will occur at 7 months following baseline visit.

5.2 Secondary Endpoints

Statistically, we will combine various measures to improve construct reliability and identify those combinations of parameters that have the highest reliabilities. Measures were targeted to address specific study hypotheses, and will be analyzed accordingly. Secondary outcomes include data obtained from the following domains:

Neurocognitive Domain:

- General Conceptual Ability from the Differential Ability Scale II (DAS-II)

Sleep Domain:

- Apnea Hypopnea Index (AHI)
- Total score from Pediatric Sleep Questionnaire (PSQ)
- Parent report of child's daytime sleepiness from a pediatric version of the Epworth Sleepiness Scale (ESS)
- Percentage of total sleep time with SaO₂ < 92%

Behavioral Domain:

- Behavior Regulation from the Behavior Rating Inventory of Executive Function (BRIEF)

Metabolic Domain:

- C-reactive Protein (CRP)
- Homeostasis Model Assessment (HOMA) for insulin resistance
- Other inflammatory/metabolic assays as identified by emerging science

Health and Quality of Life Domain:

- Total scores from the Pediatric Quality of Life Questionnaire (Peds QL)
- Obstructive Sleep Apnea Quality of Life Survey (OSA-18)

Growth Domain:

- Body mass index, weight and height, each expressed as an age, sex adjusted z-score, from direct measurement

Exploratory analyses will assess differences in AT responses among race and overweight groups in whom airway patency (and response to AT) may differ due to craniofacial anatomy and upper airway fat distribution. Analyses also will explore treatment efficacy according to the child's reported average sleep times (i.e., exploring insufficient sleep as risk factor for persistent OSA). We will also quantify the extent to which improvement in AHI correlates with improvement in other outcomes and BMI change including desaturation indices.

6. Participant Criteria

6.1 Study Population

This study will involve participation of children and their caregivers. Female and male children, ages 5.0-9.99 years of age with documented Obstructive Sleep Apnea Syndrome (OSAS) will be recruited for this study.

6.2 Inclusion Criteria

1. Ages 5.0 to 9.99 years at time of screening.
2. Diagnosed with Obstructive Sleep Apnea defined as:
 - Obstructive Apnea Index (OAI) ≥ 1 or Apnea Hypopnea Index (AHI) ≥ 2 , confirmed on nocturnal, laboratory-based PSG *and*
 - Parental report of habitual snoring (on average occurring >3 nights per week).
3. Tonsillar hypertrophy ≥ 1 based on a standardized scale of 0-4:
 - 0 = surgically absent
 - 1 = taking up $< 25\%$ of the airway
 - 2 = 25 – 50 % of the airway
 - 3 = 50 – 75 % of the airway
 - 4 = $> 75\%$ of the airway
4. Deemed to be a surgical candidate for AT by ENT evaluation.

6.3 Exclusion Criteria

1. Recurrent tonsillitis that meets published ENT clinical practice guidelines for surgery defined as: ≥ 3 episodes in each of 3 years, 5 episodes in each of 2 years, or 7 episodes in one year.
2. Craniofacial anomalies, including cleft lip and palate or sub-mucosal cleft palate or any anatomic or systemic condition which would interfere with general anesthesia or removal of tonsils and adenoid tissue in the standard fashion.
3. Obstructive breathing while awake that merits prompt AT in the opinion of the child's physician.
4. Severe OSAS or significant hypoxemia requiring immediate AT as defined by:
 - OAI > 20 or
 - AHI > 30 ,
 - Desaturation defined as SaO₂ $<90\%$ for more than 2% sleep time
5. Apnea hypopnea indices in the normal range (OAI < 1 and AHI <2)
6. Evidence of clinically significant cardiac arrhythmia on PSG:
 - Non-sustained ventricular tachycardia

- Atrial fibrillation
 - Second degree AV block
 - Sustained bradycardia < 40 bpm (> 2 minutes)
 - Sustained tachycardia > 140 bpm (> 2 minutes)
7. Extremely overweight defined as: body mass index > 2.99 age group and sex-z-score
 8. Severe health problems that could be exacerbated by delayed treatment for OSAS Including:
 - Doctor-diagnosed heart disease or cor pulmonale
 - History of Stage II Hypertension (HTN) defined as > 99% percentile (CDC prediction equations) plus 5 mmHg for either systolic or diastolic examination, based on the age, gender, and height and/or requiring medication.

Note: If Stage II HTN is noted upon examination, or at the PSG, patients will be referred for follow-up with their pediatrician utilizing the Urgent Medical Referral Form (UMRF), where BP is advised to be measured on at least two more occasions. If subsequent evaluation proves BP to be less than Stage II, then the patient may be referred for re-evaluation for entry to the CHAT study.

 - Therapy for failure to thrive or short stature
 - Psychiatric or behavioral disorders requiring or likely to require initiation of new medication, therapy, or other specific treatment during the 7 month trial period.
 - For school aged children, parental report of excessive daytime sleepiness defined as unable to maintain wakefulness, at least three times per week, in routine activities in school or home, despite adequate opportunity to sleep.
 9. Severe chronic health conditions that might hamper participation including:
 - severe cardiopulmonary disorders (e.g. cystic fibrosis, congenital heart disease)
 - sickle cell anemia
 - poorly controlled asthma (with >1 hospitalization in last year)
 - epilepsy requiring medication
 - diabetes (type I or type II) requiring medication
 - conditions likely to preclude accurate polysomnography (e.g. severe uncontrolled pain)
 - mental retardation or enrollment in a formal school Individual Educational Plan (IEP) and assigned to a self-contained classroom for all academic subjects
 - history of inability to complete cognitive testing and/or score on DAS-II of ≤ 55
 - chronic infection or HIV
 10. Known genetic, craniofacial, neurological or psychiatric conditions likely to affect the airway, cognition, or behavior
 11. Current use of one or more of the following medications:
 - ADHD medications

- psychotropic medications (antidepressants, anxiolytics, antipsychotics)
 - hypnotics
 - hypoglycemic agents or insulin
 - antihypertensives
 - growth hormone
 - anticonvulsants
 - anti-coagulants
 - daily oral corticosteroids
 - daily medications for pain
12. Previous upper airway surgery on the nose, pharynx or larynx, including tonsillectomy. *Note:* Ear surgery and/or PE tubes are not exclusion criteria.
 13. Receives Continuous Positive Airway Pressure (CPAP) treatment
 14. A parent or guardian who cannot accompany the child on the night of PSG
 15. A family planning to move out of the area within the year
 16. Female participants only: Parental report that child has reached menarche.

6.4 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 deferment:

1. Subjects currently enrolled in another intervention or longitudinal study.
2. Subjects 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. Child found to meet criteria for Stage II hypertension (defined in section 6.3 8) at the PSG or baseline visit. If subsequent clinical evaluation conducted within 30 days of initial finding indicates repeated blood pressure levels do not meet or exceed Stage II criteria, the child may be re-evaluated for study entry.
5. Child currently on a “burst” of oral corticosteroid therapy. Subject may be re-evaluated once daily oral corticosteroids are no longer prescribed and 30 days have passed since the last dose.

7. Participant Recruitment and Consent

7.1 Participant Recruitment

It is anticipated that 460 children will be recruited from participating clinical sites. The sources of referral, approaches for recruitment, and recruitment procedures will differ somewhat among the sites, according to the local structure and culture. Differences between sites are the results of variation in referral patterns and the organizational working relationship between Otolaryngology and the principal investigators. At every site, recruitment procedures will meet the local HIPAA and IRB requirements specific for that site.

The clinical sites are well established and nationally recognized for their expertise in

the diagnosis and management of OSAS in children. Sites are chosen for participation in this project based upon their knowledge, experience and referral base. Each site will collect data on PSG, neurocognitive and behavioral measures and various other data based on well established standards. Adenotonsillectomy (the intervention) will also be implemented at each site according to well established standards of care.

Other research efforts include central scoring of PSGs by the Scientific Coordinating/ Sleep Reading Center (Harvard), study management and statistical oversight by the Data Coordinating Center (University of Pennsylvania), Quality Control for Neurocognitive and Behavioral Studies and Surgical Monitoring (University of Michigan) and centralized laboratory analysis (University of Vermont Research Biochemistry Laboratory). These institutions have a distinguished track record of providing similar services for other NIH-sponsored multi-center research. As expected, this clinical trial will have oversight by a Data Safety and Monitoring Board established using NIH standards for clinical trials.

In aggregate, it is estimated that across the clinical sites, 3875 children in the targeted age range (5.0 - 9.99) per year are referred for evaluation or treatment of Obstructive Sleep Apnea.

7.2 Recruitment Specifics from each Clinical Site

7.2.1 Cleveland (Rainbow Babies and Children Hospital)

At the Cleveland clinical site, the targeted enrollment sample is 60% African-American and 50% females. Based on the local population characteristics, 1% will be Asian and 9% will have Hispanic ethnicity. Children will be recruited from collaborating ENT practices (95%) and from the clinical sleep laboratory (5%) In addition, the Metro-Health practice was added to enhance access to Hispanic children. All of the neurocognitive-behavioral and 95% of the PSGs will be performed in the General Clinical Research Center located at Rainbow Babies and Children (RB&C) Hospital with the remaining 5% of the PSGs performed in the clinical pediatric sleep laboratory located at RB&C using a montage standardized for this research. The surgical interventions take place at affiliated hospitals.

Access to target population/feasibility of recruitment in Cleveland:

The referral sample for this study derives from the RB&C Hospital and Westlake facilities (400 adenotonsillectomies/year in the age of interest), and Metro-Health (200 adenotonsillectomies/year in the age of interest). To meet the minimum study recruitment goals of 46 participants per year (over 2.5 years), the Cleveland site will perform screening PSG studies on ~100 children per recruitment-year who meet the age and co-morbidity eligibility criteria. The 100/year target represents only 16% of children in the targeted age range. Thus, achieving this goal (very conservatively) would allow for more than 80% of families to decline participation or for children to be ineligible based on co-morbidity or medication. We further assume that only 40-50% of those 100 children will meet PSG eligibility criteria (to enroll 46/year). To demonstrate Cleveland's access to African-American and overweight children, data from the RB&C pediatric sleep center were reviewed to identify the last 20 children who would have met the all CHAT inclusion and exclusion criteria. 45% of eligible children were female, 80% were minorities, and 60% were overweight- supporting the feasibility of meeting race and weight strata enrollment goals. Further evidence of the feasibility of the recruitment and retention goals is supported by the extensive research experience

of this group. In particular, the Cleveland research team has an established track record in successfully recruiting and retaining African-Americans in sleep research studies (African-American comprise 36% of the 907 children participating in the Cleveland Children's Health and Sleep Study, and 50% in the latest phase of the Cleveland Family Study.) These two research naive samples have been followed longitudinally (with repeat PSGs over time), with 72 to 85% retention rates at 5 year follow-ups. Dr. Rosen's most recent study, recruiting children from a clinical sleep lab, has resulted in 62% minority recruitment and of the 168 families contacted, 130 children (78%) were enrolled in the study, and 92% of these children underwent the two PSGs required for study completion.

7.2.2 Children's Hospital of Philadelphia

The targeted enrollment sample is 60% African-American and 50% females. Based on the local population characteristics, 1% of subjects will be Asian and 4% will have Hispanic ethnicity. Children will be recruited from both the Children's Hospital of Philadelphia (CHOP) Sleep Clinic and the Penn ENT Clinic. The Sleep Clinic evaluates more than 800 children with sleep disorders a year, of whom 40% have PSG-proven OSAS. More than 2,000 patients per year undergo adenotonsillectomy for suspected OSAS following evaluation in the ENT clinic. As an example, for July 2005, the CHOP ENT service performed 223 ATs and had 2,461 office visits. It is estimated that 25% of these children are in the CHAT age range (670/year).

Access to target population/feasibility of recruitment at CHOP:

To meet the minimum study recruitment goals of 46 participants per year (over 2.5 years), the Philadelphia site will perform screening PSG studies on ~100 children per recruitment-year who meet the age and co-morbidity eligibility criteria. The 100/year target represents only 15% of children in the targeted age range. Thus, achieving this goal (very conservatively) would allow for more than 80% of families to decline participation or for children to be ineligible based on co-morbidity or medication. We further assume that only 40-50% of those 100 children will meet PSG eligibility criteria (to enroll 46/year). To meet minimum recruitment goals of 46 participants per year per site over 2.5 years, 255 potentially eligible participants per recruitment year will be approached. It is anticipated that approximately 40% (n=102) will agree to participate, that approximately 50% (n=46) per year will have PSG findings that meet enrollment criteria, and that 40-42 (12% attrition) will complete the study.

The feasibility of meeting the weight and race recruitment goals is supported by a review of the subject characteristics among those participating in Dr. Marcus' research studies over the 18 months. In these previously research-naive subjects, 72% were African-American, 43% were female, and 37% of the OSA subjects were overweight. Most of Dr. Marcus' research studies involve polysomnography on 2 separate occasions; there has been a 95% return rate for the second study.

7.2.3 Cincinnati Children's Hospital Medical Center (CCHMC)

At the Cincinnati Children's Hospital Medical Center, children with obstructive breathing during sleep will be recruited from Otolaryngology and the sleep disorder clinics. The Department of Otolaryngology consists of 10 Otolaryngologists. Over the past 3 years, 4842 adenotonsillectomies (1600/yr) were performed in children ages 5 to 9 years, on a sample that was 52% female, 11% African-American, 7% other (Hispanic, Asian, and mixed). To meet the minimum study recruitment goals of 46 participants per year (over 2.5 years), the Cincinnati site will perform screening PSG studies on ~100 children per recruitment-year who meet the age and co-morbidity eligibility criteria. The 100/year

target represents only 6% of children in the targeted age range. Thus, achieving this goal (very conservatively) would allow for more than 90% of families to decline participation or for children to be ineligible based on co-morbidity or medication.

Access to target population/feasibility of recruitment at CHOP

The feasibility of recruiting for research studies and retaining children for subsequent PSGs are supported by a recent study of Dr Amin's where 124 children agreed to an initial PSG. 71 subjects were asked to undergo a second PSG. Of these, 53 (75%) agreed and had a second study. 48 subjects were asked to undergo a third PSG; of these, 40 (83%) agreed and had a 3rd study. 50% of the participants in Dr. Amin's pediatric studies have been overweight (BMI >85 percentile).

7.3 Sub Analysis Strata

Strata will be created and monitored such that equal numbers of racially diverse overweight children from each site are recruited and randomized across the groups (EAT and WWSC), with 60% minority recruitment from Cleveland and Philadelphia and 40% from Cincinnati..

To assure that sufficient numbers of ethnic minorities (50% African-American, Hispanic and other ethnic groups) and overweight children (50% > 95% BMI percentile) are recruited and randomized in equal proportions, children will be randomized by block design, and overweight-race specific strata will be closed once recruitment goals for those demographic groups are met.

Procedures at each site will be implemented to identify potential subjects. The procedures consist of regular review of electronic records and or medical charts according to HIPAA and institutional guidelines.

7.4 Overview of Procedures

Once potential subjects are identified the following procedures will be followed:

1. IRB approved study-related information sheets and/or educational materials will be distributed or reviewed with the parents and potentially eligible subjects to ascertain interest. These materials will either be mailed or provided to the family during their clinic or sleep lab visit.
2. Families of potentially eligible subjects 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 subjects to consider enrollment into the study.
3. The Preliminary Eligibility Determination Check List or the Child Information Worksheet (administrative tools) will be utilized and completed for potentially eligible participants. Blood Pressure (BP) values will be reviewed if available in medical history/chart to ascertain preliminary eligibility (within the prior 90 days).
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 or PSG visit at the discretion of the family and site PI.
5. Subjects who have not been evaluated by ENT for surgical eligibility within the prior 90 days will be referred to the ENT clinic for evaluation of surgical candidacy.
6. If initial eligibility criteria are met:

- 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 and scored centrally by the Reading Center.

The centrally scored PSG report will be transmitted to both the clinical site and the DCC 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 do not meet AHI/saturation criteria after central review are ineligible for participation regardless of the local clinical interpretation of the PSG data.

7. The Preliminary Screening and Screening Form (PSSF) will be completed by each site on a bi-monthly basis.

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 systemic steroids. When a child has other symptoms such as a fever or nasal/respiratory illness, the following scheduling guidelines should be followed:

- The baseline and follow-up visits/exams *excluding* PSG (see stipulations below) will not be scheduled or occur within 14 days from the time of a febrile illness

PSGs will not be scheduled or occur within 7 days from the time of:

- a febrile illness
- upper respiratory illness resulting in increased coughing
- nasal problems acutely interfering with sleep

7.5 Informed Consent

Each clinical center will be responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (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 to the parent's signature, an assent form from each participant older than 7 years of age must be signed, unless assent is waived by a local IRB.

Clinical sites will prepare an informed consent form following the guidelines of their local IRB and applicable regulations 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, subject rights and alternative treatments (refer to Appendix B: Informed Consent Template).

Prior to signing the informed consent, the research coordinator will review the details of the consent form verbally with the child and parent/guardian, and answer any questions they may have concerning participation in the study. Centrally standardized, IRB-approved informational materials (e.g. picture books, information sheets written at a

third grade reading level, for example) will be used to explain each step of the study to the child.

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. The Principal Investigator will also be available to answer questions and to inform the child and parent that participation is voluntary and that they have the right to withdraw from the study at any time without affecting their medical care.

The participant and parent/legal guardian (s) will also undergo a separate standard clinical care consent process by the ENT clinician when surgery is scheduled.

7.5.1 Optional Informed Consent for DNA/Genetic Testing

Each child and their legal guardian will be given the option to allow DNA extraction and storage for future genetic analysis on blood samples. These samples will be stored at the central repository, at the University of Vermont, as part of the CHAT study. All data will be kept confidential as outlined below and participants will be informed that a separate blood draw is not required.

7.5.2 HIPAA Authorization

Following mandated federal HIPAA regulations and according to local IRB guidelines, the use and disclosure of the subject's protected health information (PHI) 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 (e.g. 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 subject's 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 subjects from the research trial if written authorization is not provided.

At each clinical site, the process of subject recruitment must be reviewed and approved by the site's local IRB to help assure that privacy protections are consistent with federal HIPAA regulations.

7.5.3 Patient Confidentiality

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 (PID) 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 (PID) and initials only
- kept separately from identifying information used for subject 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.

8. Risks and Benefits to Participants

8.1 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 surgery) may have both greater efficacy and increased risk, which must be assured to be in a favorable balance. In this study, the risks of greatest concern are actually in the less intensive treatment arm (non surgical WWSC).

The risks of surgery are well understood and are widely considered acceptable relative to the expected (but not proven) benefit. The risks associated with delaying surgery are less well understood and are therefore of more concern. These risks will need to be balanced against the observed risks of surgery, and level of benefit seen for the surgical intervention.

A large number of treatment failures (defined in section 16) due to concerns about excess sleepiness, blood pressure elevations or general concerns by the primary health care provider would be of greater concern if coupled with an emerging demonstration of efficacy of the surgery, but would be of less concern if surgery did not seem to be having any impact on the neuropsychological/behavioral outcomes and no irreversible physical or emotional problems were being observed.

Therefore, occurrence of treatment failure leading to crossover to early adenotonsillectomy for those randomized to the WWSC arm, should not necessarily be considered a safety outcome of major concern but the DSMB will monitor the rate of treatment failure together with rates of AEs. Because specific safety issues are difficult to predict and there are many outcomes relevant to safety that we do not propose a specific monitoring boundary for safety (other than the boundary for NEPSY Attention/Executive function, which can be considered both an efficacy and safety boundary). For example, should the DSMB note an alarming elevation in blood pressure in children on the WWSC arm that could lead to an early termination recommendation regardless of interim data on NP outcomes. The DSMB will consider all reported safety outcomes and may make recommendations regarding study modifications based on their expert judgment regarding the level of concern raised by any outcome(s) and the impact on risk-benefit ratio. Refer to sections 15.2 and 17 for Reporting Guidelines (Serious Adverse Events).

8.2 Potential Risks

Subjects eligible to participate in the study have chronic symptoms suggestive of OSAS and are potential candidates for adenotonsillectomy from an experienced ENT surgeon as part of their routine clinical care. Thus, there are no serious risks to study participation above what would have been encountered during routine clinical care. Specific safeguards are in place to ensure that potential subjects with severe OSAS who would clearly benefit from prompt surgical intervention or those with clinical disorders that would be exacerbated by delayed treatment of OSAS will be excluded from participation. Children in whom an ENT surgeon has determined that immediate surgery is the proper treatment course will not be enrolled in this study.

8.3 Watchful Waiting with Supportive Care (WWSC)

The potential consequences of untreated OSAS may include behavioral, cognitive, and physiological outcomes, as described in Appendix C: Adverse Events. The 7 month wait period in children randomized to WWSC, however, is not much beyond the range (up to 6 months) encountered in some clinical practices. Finally, the time interval between symptoms onset and AT varies widely. A 7 month wait 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. As mentioned above, specific safeguards will be followed to ensure the participants safety. Regular monitoring for adverse events will also provide a mechanism for referring the child for evaluation for earlier surgery, if so recommended by an external Medical Monitor.

8.4 Surgical Intervention

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 routine care. Monitoring of surgical outcomes according to the Surgical Quality Control Manual of Procedures will be implemented by the University of Michigan.

8.5 Risks of Surgery

Surgical complications associated with the study can occur in the peri-operative period, or in the months following surgery. The following risks, most of which are extremely rare, are also outlined in the Appendix C: Adverse Events and the Surgical Quality Control Core (SQCC) Manual of Procedures.

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 (> 250 cc), 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 IV fluids or inpatient admission, hemorrhage; which may require in-patient observation admission or return to OR, 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.

Documenting and reporting of complications resulting from surgery are outlined in the SQCC Manual of Procedures.

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.

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.

Note: ENT surgeons will be informed of the PSG results for all participants who have an AHI>20, OAI>15, or marked desaturation is seen (percentage oxygen desaturation of <92% for >2% of sleep time), since these levels may influence perioperative care.

8.6 Mortality and Morbidity of Adenotonsillectomy by Site

Although AT is a commonly performed operation, with clear standardization of approaches, it is associated with a finite mortality and small morbidity. The statistics of the mortality and morbidity of this procedure by participating site, if available, are provided below:

8.6.1 Cleveland

Based on data from last 3 years on over 400 pediatric T & A in children < 12 years of age per year:

Mortalities: 0%

Morbidities:

- Post-tonsillectomy hemorrhage: 2%
- Dehydration requiring admission: 2%
- Readmission other: 0.5%
- Velopharyngeal Insufficiency: 1/3000 (0.03%)
- Nasopharyngeal stenosis: 0%

8.6.2 Cincinnati Morbidity Table

year	Total cases	Acute bleeding N (%)	Delayed bleeding N (%)	Return to the operating room N (%)
2002	2268	2 (0.09)	70 (3.09)	7 (0.31)
2003	2436	11 (0.45)	145 (5.95)	6 (0.25)
2004	2686	6 (0.22)	128 (4.77)	6 (0.22)

There was no mortality associated with adenotonsillectomy in the last three years.

8.6.3 Philadelphia

In the last 15 years, one death following AT was noted. Last year, 2100 ATs were performed, providing an estimated mortality rate of 1/20,000 to 1/35,000.

8.7 PSG Risks

Sleep monitoring requires the attachment of sensors that may rarely cause skin irritation and the study per se, may disrupt sleep the night of monitoring. Risks of irritation of PSG sensors will be minimized by using hypoallergenic materials when possible.

8.8 Risks Identified in Neuropsychological (NP) Testing

The direct risks to NP testing are fatigue and stress, which will be minimized by the use of frequent breaks; technicians will be trained on methods for identifying fatigue and being sensitive to the needs of the participants.

8.9 Other Risks

Venous sampling may cause a small bruise and occasionally result in fainting. BP monitoring may cause some discomfort associated with cuff inflation. Nasal saline spray can be irritating to the nose, occasionally causing sneezing.

8.9.1 Risks of Genetic Sampling

Information gained through analysis of genetic material is not likely to have any direct effect on the participant's health. Although highly unlikely, there is a risk of disclosure and misuse of genetic information by parties other than those directly involved with the study and identified during the Informed Consent process.

8.10 Burden to Participant

PSG and daytime study visits will be scheduled during a time when children are stable and free of acute illnesses. Testing of neurocognitive/behavioral functioning will be performed with regularly scheduled breaks during test administration to avoid excessive fatigue. To assure children are made as comfortable and relaxed as possible, Child Life personnel, with special skills working with hospitalized children and pediatric procedures, will participate in training and serve as a resource for study personnel to assure children are made as comfortable and relaxed as possible, if applicable.

8.10.1 Venipuncture

The trauma of venipuncture will be minimized by applying a local topical anesthetic to minimize discomfort. Venipuncture will be conducted by medical staff who are skilled in working with children and by those who are familiar with Child Life Principles. *Note:* A child who does not want to undergo venipuncture *is eligible* for study participation.

8.11 Potential Benefits to Participants and Others

Discussion of potential benefit to participation in the study will be presented at the time of the informed consent. There may or may not be a direct benefit to participating; however, children enrolled in the study will receive age-appropriate sleep and healthy lifestyle educational materials. Also, clinical problems may be identified that require attention. The information gained from this study may eventually prove beneficial to the treatment of other children with OSAS.

8.12 Alternatives

A discussion of alternative treatments (non-participation and adenotonsillectomy at the discretion of the ENT surgeon) will be presented at the time of informed consent. Children determined to be in need of immediate surgical treatment by the ENT surgeon will not be enrolled in the study.

9. Study Interventions

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

9.1 Sleep and Healthy Lifestyle Education

Participants in both groups will receive age-appropriate standardized educational material for both Optimal Sleep Hygiene and Healthy Habits.

9.1.1 Standardized Education Regarding Optimal Sleep Hygiene

Educational material on Optimal Sleep Hygiene will be provided to each participant at the baseline visit after research data are collected. Standardized materials recommended by the NIH NCSR (National Institute of Health, National Center Sleep Disorders) and pediatric professional sleep societies will be used to reinforce optimal sleep hygiene. Educational play will also be encouraged by providing take-home materials.

Participant and parent/legal guardian (s) will be given verbal and written directions on the use of these materials at the time of the visit. Research Coordinators will encourage and track utilization of the sleep hygiene educational tools during the course of the trial.

9.1.2 Standardized Education Regarding Healthy Habits (Behaviors)

Children and families will receive instructional material on healthy eating and daily exercise based on the most current USDA recommendations. TV viewing health messages developed by the American Academy of Pediatrics (AAP) will also be provided and reinforced with a take-home information sheet.

9.2 Other Supportive Care

Throughout the course of the trial participants identified by the principal investigator as having suboptimal asthma or rhinitis will be referred to their primary care physician for management and further treatment of these problems utilizing the Referral Form as described in the Manual of Procedures.

9.2.1 Saline Nasal Spray

All participants will receive a generic brand of an over-the-counter saline nasal spray to use as needed for nasal dryness and crusting. Proper use of the spray will be reviewed and demonstrated by the research coordinator at the baseline visit. Written instructions and a medication diary will be provided to the parent/legal guardian (s) as outlined in Appendix H of the MOP.

10. Procedures Specific to Treatment Arm Assignment

10.1 Surgical Treatment - Early Adenotonsillectomy (EAT)

Within 1 to 4 weeks (30 days) of randomization, participants randomized to the EAT arm will undergo surgery under general anesthesia, as occurs as part of routine standard of 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. 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.

10.2 Participants Randomized to Watchful Waiting with Supportive Care

Within 1 to 4 weeks after the 7-month visit, participants in the WWSC group will be referred for re-evaluation of surgical candidacy. Symptoms and PSG findings (baseline

and month 7) will be reviewed by the ENT and a decision whether to proceed with AT as part of routine clinical care will be made.

10.2.1 Ethical Considerations

A surgical sham intervention is unethical, therefore, subjects who develop new signs or symptoms indicating possible need for immediate AT or those who exceed adverse event thresholds within the blinded phase of the study (Baseline through 7 months) will be evaluated and early cross-over to AT surgery may be recommended. In an attempt to maintain the integrity of the participant's randomization assignment, the clinical data will be provided to the unblinded external Medical Monitor who will evaluate the safety and appropriateness of continued study participation and whether early cross-over to surgery should be recommended.

11. 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.

11.1 Polysomnography (PSG)

Up to two overnight visits for polysomnography will be conducted (one prior to randomization and another at 6 months), following techniques that assure standardized data collection (refer to PSG Manual of Procedures) across sites. All PSG data will be edited, scored and summarized at the Brigham and Women's Hospital Sleep Reading Center (SRC using well-developed quality assurance approaches.

11.1.1 Prior to Baseline Visit

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 SRC 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 SRC where they will be re-scored to ascertain PSG eligibility and entry into the study. If a clinical PSG has been performed more than two months (60 days) prior to baseline/randomization or was not performed using research sensors and montages, a research PSG must be performed.
2. Potential participants recruited from the ENT clinic and/or who have not undergone a PSG within 60 days prior to the baseline/randomization visit will be required to undergo a research PSG. Resulting PSG data will be transferred to the SRC within 48 hours to determine PSG eligibility and to collect research quality data to characterize baseline OSAS severity.

11.1.2 6 Month PSG Visit

Approximately 1-4 weeks prior to the scheduled 7 Month visit, all participants will undergo a research PSG. Data will be transmitted to the SRC and results will be scored (refer to the PSG Manual of Procedures).

11.1.3 PSG Standardization

Each clinical site will use a standardized approach to testing as written in the PSG Manual of Procedures. Existing PSG laboratory equipment will be utilized. Research laboratories without available capnographs will be supplemented by two Novamatrix carbon dioxide analyzers specifically for use in this trial. As a result, this will enable assessment of end tidal CO₂. Existing capnography equipment will be permitted in lieu of Novamatrix. Data will be standardized by requiring use of the same montage, comparable oximeters with some type of quality indicator (such as plethysmography waveform or perfusion index assessment) and comparable sensors, sampling rates and filters across sites. PSGs collected in clinical labs prior to enrollment may omit T3, T4 scalp electrodes. Subjects will be monitored by a certified sleep technician trained in pediatric PSG who is supervised by a lead technician certified by the SRC during central training.

11.1.4 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
- nasal problems acutely interfering with sleep

Participants will report to the sleep laboratory at least 1 hour before their usual bedtime and remain at the sleep laboratory in a quiet dark room until the study ends the following morning. Lights off will be at approximately 2100 and lights on no earlier than 0600. Children are encouraged to maintain their usual daily routine. Neither sedation nor sleep deprivation is used to induce sleep. Children will be accompanied by at least one guardian during the night. Friday and Saturday evening slots will be made available to families to facilitate recruitment by accommodating the child's school and the accompanying parent/legal guardian (s)' work schedules. At the time of the PSG, the child will undergo measurement of blood pressure, height and weight.

11.1.5 PSG Montage

Polysomnography will be collected using 17 EEG electrodes with face and scalp placements as detailed in the PSG Manual of Procedures.

11.1.6 Central Transmission of PSG Data

The PSG will be exported as a standardized electronic data file (edf) or compatible proprietary format and transmitted to a FTP server at the central Sleep Reading Center SRC for standardized scoring within 2 business days. If PSG urgent referral criteria are identified (i.e., on baseline/screening PSG, severe levels of OSAS precluding randomization; or on follow-up PSGs, levels that exceed adverse event thresholds), the data will be reviewed by the SRC Director. An Urgent Referral Alert (URA) form will be completed and transmitted to the clinical site for follow-up. The clinical site will provide this information to appropriate physicians and/or family members for clinical follow up (refer to PSG Manual of Procedures)

11.2 Morning Baseline Visit

Following confirmation of initial eligibility participants will be scheduled for a baseline morning exam 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.

The baseline visit will be rescheduled to assure testing occurs following resolution of an acute illness as described above. Exams will begin between 7:00-9:00 AM after an overnight fast of at least 10 hours duration, and the exam will 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:

- Brief orientation to testing facility and rest period
- Brief physical examination by the study physician or designee
- Resting morning blood pressures in triplicate
- Fasting venipuncture
- Anthropometry
- Breakfast and rest period
- Neurocognitive/behavioral testing and questionnaire completion
- Brief rest period
- Final eligibility confirmation
- Randomization in DMS
- Review of all take-home materials including, sleep and health education materials and use of Normal Saline Spray.

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

11.2.1 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.

11.2.2 Physical Exam

The Principal Investigator 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 oro-pharynx and oro-cavity using Friedman and Mallampati position scales and identifying abnormalities on heart, lung, neurological and ears, nose and throat assessments.

11.2.3 Morning Blood Pressure

After a 10 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.

11.2.4 Fasting Venipuncture

Approximately 20 cc of blood will be obtained by venipuncture (and no more than 3 cc/kg body weight) after a minimum 10-hour fast and after preparing the skin with a local anesthetic. Within one hour of collection, specimens will be centrifuged and serum and plasma aliquoted, with removal and storage of the buffy coat if applicable. These specimens will be stored in a -80 C freezer, following instructions outlined in the Laboratory Manual of Procedures. Assays will be stored locally and shipped on a monthly basis to LCBR. Analysis will include: insulin and glucose from plasma; and lipid profile and C-reactive protein from serum. Samples will also be stored for future testing and analysis of other inflammatory responses that may be associated with sleep apnea.

11.2.4.1 DNA/Genetic Sampling

Participants and their parent/legal guardian (s) will be given the option to consent to genetic testing of stored blood samples (section 7.5.1). If parent/legal guardian(s) provide informed consent, the buffy coat from the blood samples will be stored to permit future DNA extraction. The purpose of DNA extraction will be to identify genetic variants associated with OSAS, OSAS-related health conditions (attention deficit disorder, diabetes, hypertension, hyperlipidemia, asthma/rhinitis, tonsillar hypertrophy), or associated with surgical response to OSAS treatment.

11.2.5 Anthropometry

Children will be instructed to wear loose, lightweight clothing or change into a standard hospital gown. 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. Measurements will be repeated three times, and average values will be utilized, as defined in the Anthropometry MOP.

Information will also be collected from the maternal parent (if applicable) as follows: birth weight of child and current height and weight of maternal parent and at time of delivery.

11.2.6 Neurocognitive and Behavioral Testing

Each participant will undergo a series of cognitive and behavioral testing batteries (Table 1) conducted by a psychometrician from each site who is centrally trained and certified by the Neuropsychological (NP) Quality Control Center. Psychometricians will be supervised by a licensed psychologist and blinded to the treatment arm. Testing will be performed in a private, quiet room with adequate lighting and table space. Regularly scheduled breaks will be built into the testing sequence to avoid excess fatigue. Parent/legal guardian (s) will be asked to complete questionnaires in a separate room while their child is being tested as outlined in the Manual of Procedures.

11.2.6.1 Test Administration

Two alternative test batteries are offered to minimize the effects of test order, fatigue and circadian differences. The psychometrician at each site will alternately assign a version set (Version 1 or Version 2) to each participant as they come in for testing. Each subject will have the battery administered in the same order at baseline and follow-up exams (Month 7 and an abbreviated version at Month 12). The order of each version and the expected amount of time to complete each section is outlined in the Table 1 below and detailed in the NP Manual of Procedures. Each version set (Version

1 and 2) will begin with an “ice breaker” test, Beery-Buktenica Developmental test of Visual-Motor Integration (VMI) to acclimate the child to the testing environment.

11.2.6.1.1. Table 1: NP Testing Version Set 1 and 2

Version 1	Section Times in minutes	Version 2	Section Times in minutes
VMI	5	VMI	5
NEPSY-2 Word Generation	10	NEPSY Subtests	40
DAS-II	45	NEPSY-2 Word Generation	10
BREAK	10	CDI	5
WRAML-2 Verbal Learning	15	Peds QL	5
Purdue Pegboard	2	BREAK	10
NEPSY-2 Inhibition	8	DAS-II	45
WRAML-2 Delay	2	WRAML-2 Verbal Learning	15
NEPSY Subtests	40	Purdue Pegboard	2
CDI	5	NEPSY-2 Inhibition	8
PEDS QL	5	WRAML-2 Delay	2
Total Time to Complete	137 minutes (~2 hrs 15 min)*	Total Time to Complete	137 minutes (~ 2 hrs, 15 min)*

- Children are expected to take up to approximately 3 hours to complete the assessment.
- Parent/legal guardian should complete questionnaires in 30-60 minutes.

11.2.6.2 Description of Neuropsychological Testing

11.2.6.2.1. Cognitive Measures

- The Differential Ability Scales – Second Edition (DAS-II)* provides a standardized assessment of general intellectual functioning in children ages 2½-17 years, and has been found to be a robust indicator of neurocognitive deficits in children with primary snoring and OSAS. The School Age (ages 6+) and Upper Preschool forms (ages 2.5-6) yield highly parallel and correlated composites in General Conceptual Ability (i.e., General Intelligence), Verbal Ability, and Nonverbal Ability.
- The Developmental Neuropsychological Assessment (NEPSY)* is the most comprehensive assessment of neuropsychological functioning in children ages 3–12 years that is commercially available. The subtests of the NEPSY form five domains, two of which will be used in their entirety because of these domains have been previously established to be associated with untreated OSAS: Attention/Executive Function (Tower, Auditory and Visual Attention), and Language (Speeded Naming,

Phonological Processing, and Comprehension of Instructions). The Arrows subtest will also be administered as a measure of visuo-perceptual functioning that is independent of memory and psychomotor skills, because it has been adversely associated with primary snoring and OSAS in children. The second edition, NEPSY-2 will be available at the time that this study begins. Several subtests have been added to the Attention/Executive Function domain. Although these are new subtests have not been specifically used in studies of children with OSAS, two of them have been chosen to supplement the measurement of attention and executive functioning in the cognitive battery: Inhibition, Word Generation. A composite of these two NEPSY-2 subtests will be used as a secondary variable of interest in this study as a supplement to the primary Attention/Executive Functioning Domain Index from the NEPSY.

- c. *Beery-Buktenica Developmental test of Visual-Motor integration (VMI), 5th Edition Beery.* VMI was chosen as an initial test to introduce children to the testing environment in a similar manner across study sites. It is a simple, straight forward test measure that is generally quite enjoyable for children to complete and can incorporate substantial positive feedback. Besides its primary purpose in introducing the assessment process to all children, it also is an excellent measure of visual perception and motor co-ordination, requiring copying of drawings of increasing difficulty. It can be used with children as young as 2 years of age.
- d. *The Wide Range Assessment of Memory and Learning (WRAML-2)* is a comprehensive collection of subtests that assess new learning and memory across a broad developmental range, and is one of only a few well-validated memory tests that extend as young as age 5 years. List-learning tasks are sensitive to verbal memory deficits, especially those due to hippocampal damage or malfunction. The WRAML-2 verbal learning subtest is an update on the measure used by Rhodes et al. who documented verbal learning deficits in obese children with OSAS.
- e. *The Purdue Pegboard* will be administered as a measure of fine motor coordination, a domain that has been reported to be particularly sensitive to OSAS in adults but which has not been extensively examined in children. The task requires children to place a peg into a board using their dominant, followed by their non-dominant, hands. Appropriate norms have been developed for children ages 2 to 18.

11.2.6.2.2. Table 2: Cognitive Measures

Domain	Description of Domain	Measures
General Intelligence	Overall performance on an accepted wide-range intelligence battery.	Differential Abilities Scale Second Edition (DAS-II)
Verbal Abilities	Receptive and expressive verbal communication skills.	DAS-II Verbal Cluster, NEPSY Language Domain
Visual Perception and Construction	Ability to perceive, process, and generate motor-based or motor-free output based on visual stimuli.	DAS-II Nonverbal Cluster, NEPSY Arrows subtest, Beery VMI
Fine motor coordination	Ability to perform fluid, coordinated movements with the fingers and hand.	Purdue Pegboard
Verbal Memory	Ability to learn, retain, store, and recall new information.	WRAML-2 Verbal Learning
Attention and Executive Functions	Ability to develop, maintain and execute a flexible, future-oriented plan to meet an external goal. Integrates sustained and selective attention, response inhibition, working memory, and planning.	NEPSY Attention/Executive Domain, NEPSY-2 Inhibition and Word Generation subtests

11.2.6.2.3. Behavioral Measures

Although cognitive tests are objective and can be used to carefully characterize the specific skills that may be affected by pediatric OSAS and its treatment, it is also important to document behavioral functioning of the child. Accordingly, the assessment battery will include a multi-dimensional assessment of behavioral functioning based upon multiple reporters. As with the cognitive tests, measures were chosen based upon their psychometric strengths in this age range and known sensitivity to pediatric OSAS.

- a. *The Child Behavior Check List (CBCL)* will be administered to the parent/legal guardian (s). The original measure has been revised to include both a preschool (1 ½ to 5) and school-age (6-18) version, As many of the children will be evaluated over the course of one year and turn 6 years of age during the study, the 6- 18 year version can be used according to standard procedures.
- b. *The Behavior Rating Inventory of Executive Function (BRIEF)* will be administered to parent/legal guardian (s) and teachers to increase the ecological validity of the study by providing a neuro-psychological assessment of executive function based on “real-world” situations. It was developed to assess children ages 5 to 18 years, and yields two relevant composites:
 - Behavioral Regulation and Metacognition. The BRIEF Global Executive Composite (GEC) will be used as a secondary variable of interest in this study based on it generally being a subjectively measured analog to the NEPSY objective *Attention/Executive Function* measure.
 - *Conners' Parent Rating Scale Revised, Long Version (CPRS-R:L)*: Will be administered to parent/legal guardian and to teachers to assess the presence of psychiatric disturbance from the DSM IV criteria. It contains 80 items representing

internalizing and externalizing symptoms. The revised scales added a number of enhancements to what had long been the standard instrument for assessment of attention-deficit/hyperactivity disorder (ADHD) and its associated symptoms in children and adolescents. These improvements included symptom subscales directly related to ADHD symptoms as outlined in the DSM-IV. The subscales derived from the CPRS-R:L includes the following: Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious-Shy, Perfectionism, Social Problems, Conners' Global Index, ADHD Index, and the DSM-IV Symptom Scale. Preliminary data from Michigan suggests that the Conners' Scale is particularly sensitive to behavioral improvement in children tested three months and one year following AT.

- c. *The Children's Depression Inventory (CDI)* is a 27-item self-report measure of depressive symptoms in children ages 7-17. Although covering a broad range of depressive symptoms, the CDI's most commonly used score is a total composite. Due to the age restriction of the CDI, only children ages 7 or older will be tested with this instrument. Unfortunately, no well-validated measures of self-reported mood exist for younger children. However, because of the importance of using a self-report measure of mood (refer to NP Manual of Procedures), older children's responses to the CDI will be used in tertiary analysis of the data.

11.2.6.2.4. Table 3: Behavioral Domains

Domain	Description of Domain	Reporter			Measures
		Parent	Teacher	Child	
Behavior Regulation Difficulties	Impulsivity, acting-out, oppositional behaviors, conduct problems, aggressiveness, emotional lability, poor adjustment to change.	XXX	XXX		CBCL “Externalizing” subscales (Rule-breaking Behavior), Aggressive Behavior) <i>Parent report form only</i> . BRIEF “Behavior Regulation Index”, <i>Parent and Teacher Forms</i> ; Conners’ subscales (Oppositional, Hyperactivity, Conners’ ADHD Index, Conners’ Global Index-Restless Impulsive, DSM-IV: Hyperactive Impulsive); <i>Parent and Teacher Forms</i> .
Attention, Metacognitive Difficulties	Difficulties sustaining attention, poor planning, organization, self-monitoring, and execution of work	XXX	XXX		Achenbach CBCL “Attention Problems” subscale, <i>Parent only</i> . BRIEF Metacognition Index <i>Parent and Teacher Forms</i> , Conners’ subscales (Cognitive Problems/Inattentions, Social Problems, Conners ADHD Index, DSM-IV: Inattentive) <i>Parent and Teacher Forms</i>
Internalizing Problems	Depression and/or anxiety, manifested in subjective emotion and the behaviors and physical complaints commonly associated with these emotions.	XXX	XXX	XXX	Achenbach CBCL “Internalizing” subscale (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints) <i>Parent Form only</i> . Children’s Depression Inventory (CDI) (<i>Child self report form</i>). Conners’ subscales (Anxious-Shy, Perfectionism, Conners; Global Index: Emotional Lability). <i>Parent and Teacher Forms</i> .

11.3 Sleepiness, Symptoms of Sleep Disordered Breathing, and General Health

The following instruments will be used to assess baseline and changes in symptoms of OSAS, sleep patterns and overall health:

- a. *The Pediatric Sleep Questionnaire*, an instrument for quantifying symptoms of snoring, sleep disturbances, and sleepiness, with good internal consistency, test-retest reliability, and criterion validity in children (ages 2-18), will be used to assess baseline and change in symptoms of OSAS.
- b. A modified version of the *Epworth Sleepiness Scale (ESS)* validated on children ages 2 to 16 also will be utilized to assess level of daytime sleepiness in the study sample, from the child’s perspective. The 10-item questionnaire (including two pediatric specific items), designed to determine the likelihood of dozing during specific sedentary activities, will be administered to parent/legal guardian by the trained psychometricians in the study sample, from the child’s perspective.

- c. *Child Sleep Health Questionnaire Parent Report (Child SHQ)* will be utilized to obtain information on medical and family history, symptoms (including seasonal allergic symptoms), medicine use, and environmental tobacco since it has been previously used to describe two large community-based samples of children in the age range of the CHAT study sample.

11.4 Participant Diaries

11.4.1 Sleep Activity and Medication Diaries

To assess the possible influence of changes in sleep duration, sleep habits, and general activity over the course of the study, each parent/legal guardian will complete a sleep-activity log for 5 days recording their child's bed and wake time, major sleep awakenings, daily naps, caffeine use, and general activity levels. This log will also be used to capture over the counter and prescribed medication use, including use of the study nasal saline spray.

Parent/guardian(s) will be instructed on the proper use of the diary. Recording of sleep habits and general activity will start at the time of the baseline visit and then again prior to the 7 month visit.

11.4.2 Generic HRQL

Generic HRQL will be assessed with the Pediatric Quality of Life (PedsQL). It is shorter than the alternative (the Children's Health Questionnaire), reducing subject burden, while having excellent levels of reliability and validity in the age range under study, with evidence that it discriminates children with OSAS symptoms from controls. The 23-item tool encompasses physical functioning, emotional functioning, social functioning, and school functioning. The PedsQL has parallel child-self-reports and parent proxy report forms. Separate reports are used because child self-reports are based on perceptions of internal states, whereas parent reports reflect the child's observable behaviors. It is self-administered for parent and for children age ≥ 8 yrs. The research coordinator will administer this test for children aged 5 to 7 years.

11.4.3 OSAS Disease-Specific Health Related Quality of Life (HRQL)

OSAS Disease-Specific HRQOL will be assessed with the OSAS-18, a valid, reliable, and responsive measure that combines the advantages of a discriminative and evaluative survey in a single instrument. It consists of 18 items grouped into 5 domains: sleep disturbance, physical suffering, emotional distress, daytime problems, and caregiver concerns. The OSAS-18 also provides a direct global rating of OSAS-related QOL via a 10-point visual analog scale with specific semantic anchors. It is self-administered to caregivers. The questions are valid for ages of 6 months through 12 years.

11.4.4 Teacher Ratings

At the baseline and month 7, teachers of school-aged participants will provide independent assessment of children's behavior using the Conners' Teacher Report Form (TRF), a behavior rating scale for children age 5-18 yrs that closely parallels the (CBCL) and the BRIEF, teacher version. Solicitation and collection of teacher-report forms will be the responsibility of the scheduling coordinator. 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. If an

assessment point is to be conducted in the summer or during the 1st month of the school year, the teacher from the previous academic year will be identified and contacted.

12. Randomization Procedure

Once final eligibility is confirmed, randomization will occur. Participants will be assigned randomly to one of two treatment groups: 1) Early Adenotonsillectomy (EAT); or 2) Watchful Waiting with Supportive Care (WWSC). Randomization will be stratified by age (5.0-6.99 vs. 7.0 -9.99), weight (normal vs. > 95% BMI percentile), race and clinical sites.

For those participants assigned to the Early Adenotonsillectomy (EAT) arm, arrangements will be made by the unblinded coordinator and the ENT clinic to schedule surgery within 4 weeks of randomization.

The DCC will be responsible for providing and documenting appropriate user access to the database, preventing against unauthorized entry into the randomization system.

Each site will designate an unblinded coordinator who will have knowledge of the treatment arm assignment. The unblinded coordinator will be the only person at each site with authorization to access the electronic randomization system to obtain the treatment arm assignment.

- The unblinded coordinator will confirm final eligibility
- Randomize in the DMS
- Inform the parent/legal guardian (s) of the treatment arm assignment
- Reaffirm consent
- Reiterate the importance of maintaining the blind
- Schedule AT within 1-4 weeks, if applicable.
- Schedule WWSC Re-evaluation at the time of randomization (to occur Month 8).
- Schedule and conduct follow up visits, if applicable
- Data entry
- Maintain regulatory documents and oversee study site communications.

12.1 Maintaining Study Blind

Use of a surgical pediatric intervention prevents double blinding. A plan has been developed to minimize biases related to unblinding of investigators, psychometricians, PSG technicians and other study personnel. Preliminary eligibility will be confirmed via medical chart review (if applicable), ENT and PSG evaluations. If initially eligible, a baseline visit will be scheduled and final eligibility will be determined during the visit, after NP testing has been completed. Randomization will occur after final eligibility is confirmed in the DMS. Restricting access of treatment assignments to only the unblinded coordinator and the ENT surgeon will minimize biases. All efforts will be made to keep CHAT study personnel involved with primary data collection blinded to the treatment group (psychometricians, PSG SRC staff and site PIs). Each participant and their family will be instructed not to discuss any aspects of their treatment with the psychometricians performing the tests, the PSG technicians, and the PI during their clinical visits. It is, however, possible that such information will be divulged during testing and clinical visits. Any such instance of this

will be recorded. Personnel at the SRC will not have access to randomization codes or treatment assignments.

The unblinded coordinator will act as the liaison between the child/parent/legal guardians (s), PI, blinded site personnel and specialty core groups and should be listed as the primary contact person at each site.

13. Study Visits

13.1 Telephone Contacts

Month 2 and 5 between each study visit, , families in both groups will be contacted by phone by the unblinded coordinator for information on potential adverse events and current health status including sleep habits and AEs. The calls will also be used to reinforce aspects of optimization of medical management; reinforce healthy lifestyle, sleep hygiene, and the following of given medical plans.

13.2 Interim Clinic Visit

At 3 months, a brief interim visit will be held to measure height and weight (to assess early growth changes) and BP, obtain general symptom data and ascertain if there are any new signs or symptoms requiring further evaluation by their otolaryngologist.

13.2.1 6 Month PSG Visit

Approximately 1-4 weeks prior to the scheduled 7 month visit, all participants will undergo a research PSG. Data will be transmitted to the SRC and results will be scored (refer to the PSG Manual of Procedures).

13.3 Month 7 Clinical Visit

7 months following the baseline assessments, each participant will undergo a repeat of the NP testing and physical measurements that were conducted at baseline. These include:

- Brief physical examination by the study physician or designee
- Resting morning blood pressures in triplicate
- Fasting venipuncture
- Anthropometry
- Breakfast and rest period
- Neurocognitive/behavioral testing and questionnaire completion
- Brief rest period
- Review of 5 day Sleep Journal
- Remind WWSC families of Month 8 ENT re-evaluation visit

Techniques will be identical to those described in section 11.2, Morning Baseline Visit.

13.4 WWSC Arm Only – 8 Month Visit

13.4.1 Watchful Waiting Supportive Care Re-Evaluation

Participants in the WWSC arm will be referred for ENT re-evaluation within 1 to 4 weeks of the Month 7 Visit. Symptoms and PSG findings will be reviewed and a decision whether to proceed with AT as part of routine clinical care will be made.

13.5 Potential Treatment Failures

During the course of the trial, the unblinded 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 clinical visits (interim assessments specifically address these conditions, including questions and direct monitoring of weight and blood pressure at the 3 month visit) or as a result of study contact by the participant's family or physician (refer to section 16 for specific conditions). The unblinded Research Coordinator (RC) 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).
- Follow the general procedures for reporting SAEs (i.e., notify the DCC Project Manager (PM) within 24 hours of first knowledge of the event). Upon notification from the site, the project manager at the DCC will send the unblinded coordinator the site-specific Serious Adverse Event/Potential Treatment Failure Report Form to complete.
- The unblinded research coordinator will complete the SAE/PTF report within 48 hours of receipt. It will be submitted to the DCC and Medical Monitor simultaneously via password protected email. Instructions for completing and submitting this information will be listed on the form and details are provided in the Master Manual of procedures. Diagnostic information that will assist in the understanding of the event may be requested and follow up reports may be necessary. Significant new information on ongoing serious adverse events should be provided promptly to the DCC.
- The Independent Medical Monitor must respond to the report within 48-72 hours of receipt and will determine if the event meets Treatment Failure criteria. This information, including specific reasons for failure as defined in section 16, including why a physician involved in the child's care determined alternative therapy and which alternative therapy was needed, will be documented on the [TSTOP] CRF and entered into the data management system. If a Treatment Failure is confirmed, the unblinded research coordinator will make appropriate arrangements for further follow-up/referral (e.g., back to the referring physician). 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 CHAT steering committee's recommendations).

The Serious Adverse Event / Potential Treatment Failure Reporting Schema is provided in Appendix C.

14. Adverse Event Definitions and Reporting

14.1 Overview of Surveillance for Adverse Events and Safety Indices

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

- Families will be contacted by telephone (Month 2 and 5, 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).
- At each visit, data will be collected that includes assessment of interim symptoms (e.g., of sleepiness), school needs (special classrooms), concomitant medication use and any new illnesses or conditions that have occurred from the time of the previous visit. Also, height, weight and blood pressure data will be collected and may require further investigation if significant changes are found.
- Surgical adverse events will be captured by an intraoperative report completed by the surgeon and by questionnaires completed via a telephone interview conducted by the unblinded study coordinator at 2 and 5 months post surgery, and supplemented by information obtained at routine post-operative follow up visits or telephone calls.. Refer to the SQCC MOP for details.
- Research data will be interrogated to identify whether any laboratory or questionnaire data exceed values that indicate an abnormality.
- All treatment failures will be reviewed by the Medical Monitor and reported to the DSMB on a quarterly basis.

14.2 Urgent Medical Referral Criteria

Conditions that will generate an Urgent Medical Referral Alert (UMRA) 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. Thus, 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 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, and will be followed as described in Sections 15.2 and 17 (Follow up of Adverse Events and Serious Adverse Events).

Urgent Medical Referral Criteria include:

- Stage 2 Hypertension (> 99% for age and gender)
- Overnight sleep time in desaturation of < 90% for > 2% of sleep time, OAI >20 or AHI > 30
- CDI score of > 70
- DAS-II- score of ≤ 55 on summary IQ.

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, as well as others identified in Appendix C, will also be reported as Adverse Events.

An *Urgent Medical Referral Alert* should be completed within 24 hours of first knowledge of the event.

14.3 Patient Safety and Maintaining Study Blind

In order to minimize potential risks to the participant's safety while also maintaining the integrity of the study blind, the unblinded coordinator will act as the liaison

between the child/parent/legal guardians, all blinded site personnel and specialty cores. It will be the unblinded coordinator's responsibility to assist in the protection of the patient's safety through child/parent/legal guardian inquiry at each contact. The unblinded coordinator will also be responsible for entering these data into the DMS. Such data will be considered *preliminary* until the PI confirms and signs off on these data after the 7 month visit. This will help to protect the integrity of the study design by not exposing blinded site personnel to the data. The exception will be in the cases when the PI must be notified in order to assist with communications regarding medical management. These conditions include all SAEs and Treatment Failures (after confirmation of the latter by the Medical Monitor.) The Principal Investigator's responsibility will be to assure that appropriate study data are communicated to the participant's family and physicians and that appropriate referrals or interventions are initiated.

15. Definitions

15.1 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings or abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

15.2 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 and listed in Appendix C 3: Adverse Events).

15.2.1 Expected (Anticipated) Adverse Events

Adverse events that are expected and are identified in the protocol and for the purpose of this study have been identified as:

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

15.2.1.1 Foreseeable (expected) events that may not qualify for AE 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 (refer to Appendix C-1). Since the surgical procedure (AT) is being performed as part of routine 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 including those associated with surgery (AT) that do not exceed threshold definitions as defined in Appendix C-3 will not be considered adverse events and will not warrant reporting.

Associated with PSG

- Skin redness from removal of adhesives
- Temporary depigmentation under area of sensor attachment
- Poor sleep during PSG

Associated with AT

- Post-op sore throat < 21 days
- Post-op hoarseness and difficulty swallowing < 21 days
- Intra-operative blood loss <250 cc and/or post-op blood tinged oral or nasal secretions *for < 72 hours*
- Velopharyngeal Insufficiency (nasal regurgitation or hypernasality) lasting < 2 months and not requiring specific evaluation or intervention

Associated with Phlebotomy

- Temporary Pain
- Fainting without Injury

Other

- Sneezing from nasal spray
- Nasal bleeding (small, temporarily associated with nasal spray)
- Anxiety surrounding testing

15.2.1.2 Foreseeable (expected) events that exceed threshold definitions and warrant reporting

Foreseeable events that warrant reporting have been identified by each specialty group involved with the study. Adverse Events that warrant reporting are those that exceed the threshold definitions listed in Appendix C-3.

15.2.2 Abnormal Laboratory Values

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.

Laboratory Alerts:

The LBCR will report the following lab results directly to the site PI for follow up. The tests will be repeated locally to confirm.

- Fasting blood sugar > 126 mg/dl
- Lipid Panel:
 - Total cholesterol > 200mg/dl

- o LDL cholesterol > 130 mg/dl
- o HDL cholesterol < 35 mg/dl
- o Triglyceride > 150 mg/dl

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.

15.2.3 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.

15.2.4 Unanticipated Problem Involving Risks to Subjects 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 subject's participation 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 (refer to Appendix C for complete details).

15.2.5 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.

15.2.6 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.

15.3 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 (s), other than those expected and identified in Appendix C-3 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.

15.3.1 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 in CHAT. 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.

15.4 Follow Up of 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 case report form according to the instructions outlined in the Manual of Procedures.

SAEs (refer to section 17) 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.

15.4.1 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.

16. Treatment Failure

Conditions that may require additional/alternative therapies that may or may not be exclusionary criteria and are designed to minimize the potential risks to participant's safety:

- 1) Child's physician has identified a change in signs or symptoms that in his/her opinion warrant alternative treatment for OSA. Examples of such changes in clinical status include:
 - new academic or behavioral problems resulting in a recommendation for grade retention
 - special education

- counseling or placement on medications for behavior, or emotional problems
 - new medical problems including 3-5 below
- 2) 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 chart documentation of 3 culture positive infections will be 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 RC and paid for by the study.
- 3) New clinical diagnosis of cor pulmonale
- 4) Development of “failure to thrive” defined by weight loss during the course of study follow-up characterized by:
- i. Weight falling below the 3rd percentile for age and gender **OR**
 - ii. Weight falling by two or more major isobars on the weight for age CDC percentile charts (<http://www.cdc.gov/growthcharts> **AND**
 - iii. The weight loss is not better explained by either an intentional weight loss (as part of healthy life style changes) or a transient loss related to an intercurrent acute illness such as viral gastroenteritis.
- Note:** this definition excludes children whose baseline BMI is \geq 85% for age and gender.
- 5) New onset of Stage 2 hypertension that is not better explained by another medical condition (for example, nephrotic syndrome).
- 6) New-onset hypersomnolence defined as reports of falling asleep on average > 3 times per week at school (not planned naps) despite spending adequate time in bed overnight (at least 10 hrs per night) that is not better explained by other factors unrelated to OSA (for example, intercurrent use of a new medication such as a sedating antihistamine). *These criteria only apply to children attending school.*

16.1 Treatment Failure Defined by Arm

Those conditions that may require alternative therapy during the 7 month study and classified as treatment failures (in addition to those listed above) are described below:

Note: If alternative treatments are required, regardless of treatment arm assignment, the participant will remain in the study and followed until all visits and procedures have been completed through the 7 month trial period.

16.1.1 Early Adenotonsillectomy (EAT)

- Initiation of Continuous Positive Airway Pressure (CPAP) after AT surgery.
- Additional AT surgery, as clinical indicated.

16.1.2 Watchful Waiting Supportive Care (WWSC)

- Cross over to AT surgery for any of the reasons listed above.

- Initiation of Continuous Positive Airway Pressure (CPAP).

Parent/legal guardian (s) who decide that they no longer want to wait 7 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.

17. Reporting Serious Adverse Events

The clinical site is responsible for reporting SAEs to the DCC within 24 hours of first knowledge of the event via telephone or email followed by completion of the SAE/PTF form and corresponding case report form [AE] within 48 hours. The unblinded coordinator will maintain a copy of these reports in a secure location. Report SAEs to the Data Coordinating Center:

CHAT Project Manager
 University of Pennsylvania School of Medicine
 Center for Clinical Epidemiology and Biostatistics, CRCU
 3535 Market Street, Suite 560
 Philadelphia, PA 19104
 Phone: 215.573.0172 Fax: 215.573.6262 or *Email* : lacyk@mail.med.upenn.edu

In the event that the Project Manager is not available contact:

Rosemary Madigan, RN, MPH
 Phone: 215-573-6314 Fax: 215.573.6262 *Email*: rmadigan@mail.med.upenn.edu

At the time of the initial report, the following information should be provided as described on the SAE/PTF reporting form and AE case report form:

- Study identifier (CHAT)
- Study Center ID/Research Coordinator ID
- Participant Identification Number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was altered
- Reason why event is classified as serious
- Investigator assessment of the association between the event and study treatment (refer to MOP for specific guidelines)

Within the following 48 hours, the unblinded research coordinator must provide further information on the SAE in the form of a written narrative. This should include a copy of 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.

In addition, the site must promptly report all SAEs to their IRB via written, dated notification in accordance with the IRB's reporting requirements. Copies of all such correspondence must be maintained in the clinical site's regulatory binder.

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

as required including, but not limited to, the University of Pennsylvania's Office of Human Research, the DSMB Chair, and the NHLBI Program Scientist within 7 days of its occurrence. DCC will also provide follow up reports.

18. Medical Monitoring

18.1 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, the unblinded research coordinator and ENT surgeon (if applicable) will have the primary responsibility of overseeing all adverse events, and will ascertain their *preliminary* relationship to study participation, and coordinate follow up when applicable. This will include careful assessment and appropriate reporting of adverse events.

Medical Monitoring will also include oversight by the Data Coordinating Center generating reports through regular assessment of the number and type of SAEs (refer to the Master Manual of Procedures for the type and frequency of reports).

There may be cases when the PI must be notified in order to assist with communications regarding medical management. These conditions include all SAEs and Treatment Failures (after confirmation of the latter by the Medical Monitor.) The PIs responsibility will be to assure that appropriate study data are communicated to the participant's family and physicians and that appropriate referrals or interventions are initiated.

18.2 Independent Medical Monitor

A pediatrician unassociated with any clinical site, will serve as the Independent Medical Monitor (IMM). The IMM (or alternate) will have access to randomization codes in order to make an informed decision about the safety of a particular participant when a health care issue arises that warrants immediate attention. In addition to aggregate data, the IMM will receive reports of all AEs that are:

- Expected and exceed thresholds
- Unexpected and Serious
- Unanticipated Problems that fit the reporting criteria (listed in Appendix C)

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 IMM 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.

19. Serious Adverse Event and Unblinding of Treatment Arm

If there is an SAE, which is thought by the Medical Monitor 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. The medical monitor will determine if unblinding is necessary after consultation with the PI and ENT. 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, NHBLI) 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 right away.

19.1 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 (SSTOP) 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.

19.2 Other Study Medical Monitoring and Reporting

19.2.1 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 outlined in Appendix C will be reported (as required by institutional IRBs). The DCC will report complications from surgery to the SQCC, 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 SQCC or the DSMB). Dr Garetz, Director of SQCC, will initiate an investigation. Actions may include ongoing monitoring, retraining, excluding the participation of specific surgeons, or excluding specific sites.

19.2.2 Severe OSAS Symptom Monitoring through PSG

19.2.2.1 Baseline

Severity of OSAS will be determined by PSG review at the central reading center. Any PSG study meeting Urgent Medical Referral Criteria (section 14.2) will be identified and confirmed by the Director of the Sleep Reading Center. . Within 24 hours of knowledge of documenting severe OSAS that meet SAE reporting, the SRC will electronically transmit the URA to the site's coordinator and PI, who will facilitate appropriate clinical management and follow up. Children who meet at least one of the UMRC identified during the screening PSG will not be eligible for randomization and providing such data to the PI will not contaminate outcomes. In addition, surgeons will be informed of the baseline research PSG for children randomized to EAT if the AHI>15 or marked desaturation is seen (percentage oxygen desaturation of <92% for > 2% of sleep time), since these levels may influence perioperative care.

19.2.2.2 Follow Up

Data from follow-up PSGs will be available at a time when all 7 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.

19.2.3 Metabolic Monitoring

If extreme levels of cholesterol or triglycerides are noted or abnormal fasting glucose levels on laboratory sample analysis, with confirmation on repeated analysis of the same sample, the family and child's physician will be notified with suggestions for repeating the test on another day, and if persistently abnormal, for referral for evaluation of hyperlipidemia or glucose dysregulation. Abnormal values will be communicated to the Independent Medical Monitor who will determine the safety of continued study participation or the need for unblinding.

19.2.4 Laboratory Alerts

Glucose dysregulation and dyslipidemia (American Heart Association; Circulation; 2003: 107:156-1566) will be reported directly to the site PI for follow-up testing. Refer to Section 151.2 and Appendix C-3 for details.

19.2.5 Neuropsychological Monitoring

Psychometricians will review the child's response to the CDI prior to the child's discharge from the research center. Children who endorse a suicidal intent on the CDI *or have* a total CDI score of > 70, will be identified to the site's licensed psychologist assigned to the study. If a child answers positive to the question: "I want to kill myself", the psychologist will contact the PI and an URA will be made. Children who are deemed at imminent risk of suicidality will be referred to the nearest psychiatric emergency center. If a child does not note an immediate intent for self-harm, the parent/legal guardian (s) will be given mental health referral information. These data will be shared with the Independent Medical Monitor who will determine the safety of continued study participation or need for unblinding.

If NP testing reveals a DAS-II summary score of ≤ 69 (summary IQ), the parent/legal guardian (s) will be notified and the participant will be referred to his primary physician. A Medical referral form must be completed.

20. Participant Refusals, Screen Failures, Withdraws, Discontinuation and Missed Appointments

20.1 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.

20.2 Screen Failures

Potential participants who do not meet one or all of the following are considered screen failures and will not be enrolled into the study:

- Not suitable for surgery *or* delay in surgery as determined by ENT
- Overnight sleep time in desaturation of < 90% for > 2% of sleep time, OAI >20 or AHI > 30
- Inability to complete cognitive testing
- DAS-II score of ≤ 55 on summary IQ
- Stage 2 Hypertension (> 99% for age and gender)

20.3 Withdraw/Premature Termination

In the event that a participant withdraws/terminates from the study prior to the 7 month clinical 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.

20.4 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 (s) 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
- Quality Assurance

20.5 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, SCC/SRC and NP staff. The Quality Control Procedures are detailed in the Manual of Procedures for each specialty group.

20.6 Centralized Training

Training will be provided to all key study investigators and staff (coordinators, research assistants, lead sleep technicians) and leaders of quality control committees. Joint introductory sessions will be held that include review of the entire protocol and study organization and allow all study personnel to become acquainted. Breakout sessions are held that focus on specific aspects of data collection and database management: PSG; BP; Anthropometry; NP testing, other questionnaires, Recruitment and Retention; Safety Monitoring; Follow-up; Surgical Intervention; Data Entry and Data Queries; Ethical Issues; Special Procedures for Studies of Children (including Child Life procedures). Time also is allotted to document proficiency in specific procedures (e.g., PSG, BP, data entry), which may require combinations of observation by the trainer and written exams.

20.7 Certification Processes

Most procedures (NP testing, BP, PSG, anthropometry) 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 (PSG), and submission of successfully completed studies during pilot studies (meeting standards for quality and completeness when evaluated by the relevant Quality Control group). 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 (e.g. 2 in one month), the PI will be notified and procedures for remediation be implemented (for completion of additional practice studies, re-training or removal from the study).

21. Administrative

21.1 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 of the protocol and the informed consent form must be obtained and forwarded to the University of Pennsylvania Data Coordinating Center prior to screening or enrolling any subjects. The clinical site's Principal Investigator also maintains the responsibility of 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. The required elements of the consent form are included in Appendix B.

21.2 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.

21.3 Record Keeping

21.3.1 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, pharmacy dispensing records, 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.

21.3.2 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study and all data requested on the CRF must be recorded. Samples of each form and directions for completion are provided in the Manual of Procedures and study-designated personnel (scheduling coordinator) from each site will be trained in Case Report Form completion and entry into the DMS.

21.4 Record Retention

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

22. Data Management and Analysis

22.1 Data Management and Quality Assurance

The DCC will coordinate all CHAT activities pertaining to:

- Design, development, production, testing, and distribution of electronic CRFs
- Collection, entry, verification, validation and query resolution of data

Data management issues, especially those concerning data quality and integrity in multi-center trials will be addressed within the MOP and emphasized during the RC training prior to protocol initiation.

The DCC will develop and maintain a computerized Data Management System (DMS) 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 DMS tools available on the workstation. A manual back-up system for participant randomization will be implemented in the event the DMS system is not available.

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.

22.1.1 Database Administration and Access

The DCC will be responsible for providing and documenting appropriate user access to the study database, preventing against three major sources of data security problems: unauthorized internal access to data, external access to data and malicious intent to destroy data and systems.

The database administrator of the DCC will be responsible for optimizing database performance, reliability, and backup of data. External, unauthorized access to data will be prevented through cooperative efforts of the DCC database administrators and network and system administrators.

22.2 NHLBI Data Sharing Policy

The NHLBI has strict guidelines regarding Investigator access to study data and data sets during the course of the trial to assure that the confidentiality and privacy of study participants is protected. An explanation of Investigator responsibilities when seeking access to study data is explained in NHLBI: Policy for Distribution of Data: Appendix D and on the NHLBI website at www.nhlbi.nih.gov/resources/deca/policy_new.htm.

The SRC will develop a web portal for web-based sharing of de-identified PSGs and group level covariate data as has been done for other multicenter study

23. Study Monitoring, Auditing, and Inspecting

23.1 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.

23.2 Study Monitoring Plan/Site Visits

DCC will provide oversight and monitoring according to the plan outlined in the MOP. The investigator will allocate adequate time for such monitoring activities and ensure that the monitor or other compliance or quality assurance reviewers are given access

to all study-related documents and study related facilities (e.g. GCRC including sample storage facility and Sleep Lab/Clinic and other areas if necessary). Adequate space to conduct the monitoring visit must also be provided.

Each specialty core center involved with the study (NPQA, SCC/SRC, SQCC and LCBR) will provide an additional layer of quality control and monitoring as listed in the MOP(s).

23.3 Site Visits

Within 3 months of initiating data collection, each site will undergo a formal site visit by a team that will include members from the DCC, SCC/SRC, NPQA, and SQCC, if appropriate. One member from an alternative clinical site may also participate. Site visits generally last two days (including one night observing the PSG hook-up) and are designed to identify early in the study any departures from protocol, as well as to provide positive reinforcement to the staff and further improve the bonding among staff from various study components. 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.

23.4 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. GCRC, 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.

23.5 Independent Data and Safety Monitoring Board (DSMB)

A DSMB will be established according to NHLBI policies. Members will include experts in sleep medicine, otolaryngology, biostatistics, pediatrics, neurocognition; and ethics (some overlapping). They will be selected from institutions independent of any participating site. Each proposed member, and his/her background and areas of expertise will be provided to each site's Institutional Review Board (IRB) and the NHLBI. The DSMB will convene to review the final protocol and DSMB Charter before study initiation and then periodically, and not less frequently than annually. The DSMB will be consulted as needed to address issues reported to the Medical Safety Officer, any deviations from the protocol, and adverse events.

23.6 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. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects will be provided with a consent form describing the study and providing sufficient information to make an informed decision prior to entering. A template of the Informed Consent is provided in Appendix B. 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.

24. Statistical Plan

24.1 Summary of Study Design

The proposed study design is a two-arm randomized clinical trial to assess the effects of AT surgery in children with OSAS. Approximately 460 eligible patients will be randomized to one of two arms (EAT or WWSC, 230 per arm) and followed for 7 months. The primary outcome, which will be measured at 7 months, is neurocognitive functioning, specifically executive/attention functions. Although there are many secondary outcomes of interest, the secondary analysis will concentrate on 12 key outcomes. Sub-group analyses that analyze the effects of AT surgery by race and weight.

24.2 Planned Power and Sample Size Determination

The primary efficacy hypothesis relates to improvements in neuropsychological functioning as defined by the attention/executive domain score (AEDS) of the NEPSY in the EAT group as compared with the WWSC group at the end of the 7-month period of observation.

Data from O'Brien et al., comparing children with and without OSAS showed an effect size of 0.6 for a test of cognitive function. In preliminary data reviewed in the SCC application, tests parallel to the NEPSY showed improvement one year after AT in a sample of 30 children with an age and AHI in a comparable range to that of the targeted sample, with effect sizes of 0.43 (CMAS numbers, an attention test) and 0.59 (Category test, an executive function test). We are planning a sample size of 200 patients per arm, permitting us to achieve approximately 90% power for detecting an effect size of 0.33 for both the CMAS/attention test and the Category/executive function test. Since some dropout is inevitable, the planned sample size will be expanded somewhat to compensate for such loss (although we recognize that potential bias associated with dropout will not necessarily be fully mitigated by expanding the sample size by an amount that simply ensures that 200 patients per arm complete the study).

The effects of AT will be evaluated separately in subgroups of race and weight, as OSAS may be more common in some ethnic groups and in overweight children. These subgroups, and the impact of AT may differ from that seen in white and non-

overweight children. Assuming 50% of the study sample is of a diverse race/ethnic background and 50% are overweight, approximately 100 patients per arm will be available for these subgroup analyses. This sample size will provide upwards of 90% power for detecting effect sizes of 0.45 and above in any such subgroup, and should be adequate for assessing substantial treatment by race and/or treatment by weight interactions. Such interactions will be assessed both by evaluating treatment differences in subgroups, and through regression models that include interaction terms.

There are many secondary outcomes of interest that will be analyzed. However there are 12 secondary outcomes that are considered the most important in assessing the efficacy of AT in OSAS children. In Table 5 we list the 12 most important secondary outcomes and summarize the results of power analyses based on available data. Note that there is limited data on pre and post AT measurements in this population. Thus the secondary outcomes are listed based on whether pre and post AT data in OSAS children similar to the targeted population is available. Pre and post AT on OSAS children is available for AHI, total score of the Pediatric Sleep Questionnaire, total score of the General Conceptual Ability (GCA) of the Differential Ability Scales (DAS-II), Behavioral Regulation total score of the BRIEF, total score of the OSAS-18 survey and weight z-scores. We used these data to estimate the change from baseline to 7 months in the EAT group (sources given in column 4). We assume that the change from baseline to 7 months in the WWSC group is zero. Thus, the Δ in Table 5 for the first five secondary variables represents the change from baseline to 7 months between the two arms; in all cases 80% and 90% power is achieved based on the available pre and post AT data. In most cases there is no information available to estimate the correlation between pre and post AT. We assume (conservatively) the correlation between pre and post AT is 0. The exception to this is available data on correlation between pre and post AT for the Behavioral Regulation total score from the BRIEF. In a study conducted in Dean Beebe's lab, they found the correlation between pre and post AT for BRIEF to be 0.9. The Δ presented in Table 5 are based on this correlation value of 0.9, but we also conducted power analyses using a correlation value equal to 0.8 and 0.0 and found the Δ needed to achieve 90% power based on these correlations are 1.9 and 4.3, respectively.

For the other most important secondary outcomes, the only available data are estimates of means and standard deviations from observational and cross-sectional studies on OSAS children similar to the CHAT targeted population. We consider these estimates as the baseline estimates of these secondary outcomes. Therefore the Δ in Table 5 gives the unit change from baseline (Pre-AT) to 7 months (Post-AT) in the EAT group to achieve 80% and 90% power. Again we assume the correlation between baseline and final measure is 0.

Continued on next page.

24.2.1 Table 5: Power Analysis: 12 Secondary Outcomes

Secondary Outcomes	Δ for 80% Power	Δ for 90% Power	Source of Data
Pre and Post AT Data Available			
AHI	0.39	0.45	SCC application C.2.2 Chervin
Pediatric Sleep Questionnaire (total score, SRBDS)	0.06	0.07	Chervin et.al. Pediatric Sleep Questionnaire; Prediction of Sleep Apnea and Outcomes, in press
GCA total score from DAS-II	5.7	6.6	SCC application C.3.1 Louisville
Behavioral Regulation Total Score from BRIEF	1.2	1.4	Beebe study, unpublished data
OSAS-18 (total score)	0.46	0.54	Goldstein, et.al. Arch Otolaryngol Head Neck Surgery, 2002; 128: 770-794
Change weight z-score	0.56	0.64	Marcus, et al. J Pediatr, 1994; 125:556-562. (no data on height and BMI z-score)
Observational Data Available			
Epworth Sleepiness Scale	2.0	2.3	Melenderes, and Marcus. Pediatrics, 2004; 114: 768-775
% of total sleep time with SaO2 < 92%	0.48	0.56	Redline study, unpublished data
CRP	0.18	0.21	SCC Application C.7 Cleveland
HOMA	0.20	0.23	SCC Application C.7 Cleveland
PedsQL (total score)	Parent: 7.7 Child: 7.3	Parent: 8.8 Child: 8.3	SCC Application C.5.16 Louisville

Δ = unit change from baseline to 7 months between the two arms (EAT and WWSC) needed to achieve 80% or 90% power

24.3 Statistical Analysis

Primary analyses will follow the “intention-to-treat” principle: individuals will be analyzed according to their assigned treatment group, whether or not they remain on the assigned treatment. 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. Several methods are available to analyze data when some are missing, from simple methods like last observation carried forward to the multiple imputation approach, but there is no consensus as to a preferred method. Thus, several different analytical methods will be used, include those mentioned, to assess the sensitivity of conclusions to the analytical approach.

A large number of behavioral and functional outcomes may be affected by AT. We will be performing multiple analyses to investigate the association of these variables with AT, and with each other. These analyses will be exploratory, and their interpretation will be in the nature of hypothesis generation; therefore we will not impose any adjustments for multiple comparisons. When interpreting patterns of response, we will place greater weight on findings that are internally consistent (i.e.,

highly correlated indices measuring the same or similar constructs). We do not, however, anticipate that measurements across all domains (e.g., physiological vs. functional) will provide consistent patterns of response. In these cases, the strength, variation, and consistencies of responses will aid interpretation of such patterns.

In addition to the analyses described subsequently, descriptive statistics will be used during the course of the study as part of data management procedures for monitoring data quality. A brief overview of the statistical methods that will be used at the time of analysis, both for descriptive purposes and in more comprehensive analysis of the primary research questions, is summarized in the following sections.

24.3.1 Descriptive Analyses

Standard descriptive statistics will be used to summarize baseline characteristics and study outcome measures at each follow-up visit, both overall, and within each treatment group. Examination of baseline characteristics will include estimates of the distribution of age, race, weight status (normal vs. overweight) and other demographic characteristics, baseline AHI and other sleep indices, neurocognitive, behavioral, metabolic, growth, blood pressure, and health QOL. Summary statistics such as means, medians, and ranges will be produced for all measures. Frequencies and percentages will be computed for all categorical variables. Graphical methods including stem-and-leaf diagrams, quantile-quantile plots, scatterplots, and boxplots will be used to examine distributions and identify potential influential points. The balance of baseline measures across the two treatment groups will be compared using appropriate 2-sample tests, including Wilcoxon rank-sum and t-tests, and Fisher's exact and Pearson Chi-square tests.

24.3.2 Analysis of Primary Outcome

The primary analysis comparing the change in the NEPSY Attention/Executive Functioning score between the EAT and WWSC groups will be performed using Analysis of Covariance (ANCOVA) adjusting for the stratification factors of race, weight status, and site. Change will be defined as the difference between the 7 month and baseline responses. Secondary analyses of the primary outcome will rely on linear regression to evaluate whether observed differences, if any, are attributable to imbalances in prognostic factors such as baseline AHI. Additional analyses will be performed adjusting for other potential confounding variables such as gender and baseline values of BMI, neck size, and season of study entry and cognitive, behavioral and laboratory indices, but these will be subsidiary to the primary comparison. Standard regression diagnostics will be used to assess model adequacy, and to examine potential outlying or influential data points.

24.3.3 Analysis of Secondary Outcomes

A number of secondary analyses will be conducted, both to evaluate the secondary outcomes, and to supplement the primary outcome comparison. The most important secondary outcomes include AHI, total score from Pediatric Sleep Questionnaire, child self report of daytime sleepiness from Epworth sleepiness scale, and percentage of total sleep time with $\text{SaO}_2 < 92\%$ (sleep domain), the General Conceptual Ability from the DAS-II (neurocognitive domain), Behavior Regulation from the BRIEF (behavioral domain), CRP and HOMA (metabolic domain), and the Total scores from the PedsQL and OSAS-18 (health QOL domain). Included in the list of secondary outcomes is the NEPSY A/E change from baseline to the 7 month follow up visit.

Methods as described for the primary outcome will be used to evaluate the secondary outcomes as defined as the change from baseline. As above, standard regression diagnostics will be used to assess model adequacy, and to examine potential outlying or influential data points. The distribution of AHI, percentage of total sleep time with $\text{SaO}_2 < 92\%$, average variability of CRP are skewed. Therefore we will utilize the natural logarithm transformation of the change in these variables in the analyses that include these variables. In addition to treating AHI as a continuous secondary outcome, it will also be expressed as a binary variable defined a couple ways. First, based on the adult literature, an outcome of 50% reduction at 7 months, and second to quantify the proportion of children with a 7 month change to an AHI < 2 and OAI < 1 . Withdrawal rates will be compared between arms using standard methods for categorical data.

24.3.4 Analysis of Secondary Objectives

The additional secondary objectives focus on quantifying the extent to which the magnitude of improvement in functional and physiological outcomes can be predicted by the extent to which improvement in overnight breathing disturbances (i.e., AHI), oxygenation parameters and sleep consolidation (i.e., sleep efficiency and OAI). In these analyses, which will be observational and therefore not based on “intention to treat”, the outcomes will include the primary NEPSY A/E, as well as indices that describe behavior, QOL, blood pressure, metabolic profile, and growth. These will be expressed as continuous outcomes. The exposures (independent variables) will be based on summary values from the PSG performed at baseline and the end of the 7 month treatment period. A linear mixed effects model, with random intercepts and slopes, will be implemented to estimate the magnitude and direction of the association between the various changes in sleep parameters (e.g., change in AHI) and changes in functional outcomes (e.g., NEPSY A/E score). The slope will be defined to characterize the change in a specific outcome, and regressed on overnight breathing disturbances, oxygenation parameters, and sleep consolidation. Each model will include relevant baseline covariates (e.g., race, gender) as well as time dependent covariates (e.g., BMI).

24.3.5 Subject Population for Sub-Analysis

Because there are data suggesting that reductions in OSA severity following AT may be attenuated in children who are overweight and of diverse race/ethnic groups, the assessment of the effects of AT across these subgroups are of interest in this study. Statistical tests of treatment by covariate interaction will be performed by extending the ANCOVA models described above. Testing within the subgroups will be performed whether or not significant treatment by covariate interaction is found. The predictive value of overweight and race on treatment effect will be assessed in the overall study population using linear regression methods. In addition, we will perform direct comparisons of change following AT in racial subgroups. These comparisons will be observational in nature, as they will consider only those randomized to EAT. An attempt to reduce the effect of confounding variables in these observational analyses will be done by adjusting for covariates that are known predictors of cognitive function and that are associated with race, such as socioeconomic status (using family income and maternal education level). These subgroup analyses and assessment of predictors are exploratory only.

24.4 Monitoring and Interim Analyses

The study will be monitored routinely for issues of safety, data quality and study conduct (including recruitment and dropout rates). The NEPSY A/E measure, our primary outcome, will be the primary focus of planned interim analyses of efficacy and safety. This is an objective measure which is sensitive to a broad range of cognitive insults, including exposures associated with OSA. Early demonstration of a substantial effect on this measure would be supportive of the established wide use of AT in this population of children and thus delay in implementing such surgery could be considered to present a safety concern as well. A large benefit as measured by this parameter could therefore appropriately lead to early termination of the study in the absence of major inconsistencies with important secondary efficacy outcomes or other major safety concerns.

We will perform two interim analyses, after one-fourth and one-half of the study population have completed their 7-month evaluations. The CHAT timetable assumes recruitment of 16 patients per month, so that approximately one-fourth (n=115) and one half (n = 230) of the participants will have been accrued and followed for 7 months at months 14 and 22, respectively. The results of these analyses will be presented to the Data Safety and Monitoring Board (DSMB).

We will use the methodology of O'Brien and Fleming to establish monitoring guidelines based on finding a statistically significantly greater change in the NEPSY A/E score in one group compared to the other. Assuming looks at 14 and 22 months we will have data on 115 and 230 participants, respectively, corresponding to information proportions of 25% (50%). The boundary significance level to which the observed p-value will be compared are 0.0014 and 0.0102 at each of the interim looks, respectively, with the threshold significance level for the final analysis adjusted to 0.046. This boundary has the property of being very conservative at the first look, when the estimates are unstable, and much less conservative at the second look, when greater stability of estimation is anticipated. In addition, the Lan-DeMets alpha-spending approach will be used to allow flexibility if the DSMB asks for additional interim analyses. The DSMB will make recommendations about continuing or early termination to the NHLBI, based on these considerations, status of secondary efficacy and safety measures, and their expert judgment.

24.4.1 Treatment Failure

In addition to monitoring the NEPSY A/E, we will closely monitor the rate of treatment failure (defined as below) as a key outcome with respect both to safety and feasibility. If 10% of children assigned to WWSC drop out to obtain surgery, the efficiency of the study (based on an intention-to-treat analysis) will be reduced by approximately 20%; that is, our "inflation factor" of 15% will not be quite adequate to compensate for these crossovers, and the study will have reduced power to detect the pre-specified effect. If as many as 15% of children on the WWSC arm cross over and receive surgery early, the efficiency will be reduced by more than 40%. (These projections assume that we will be able to continue to follow those who cross over and obtain the primary outcome data at 7 months, and that they will exhibit the same effect as those assigned to the AT arm.) If a rate of crossover between 10 and 15% is observed at 2 successive interim reviews, the study team will propose an increase in sample size to account for the dilution of the effect size that could be observed. If a rate of crossover greater than 15% is observed at 3 successive meetings, or a rate of greater than 20% is observed at 2 successive meetings, and the team cannot

describe a credible plan to reduce this rate, consideration may be given to terminating the study due to the reduced likelihood of establishing anything but a very large effect.

25. Study Finances

25.1 Funding Source

This study is financed through a grant from the US National Institutes of Health, National Heart, Lung, and Blood Institute.

25.2 Subject Payment

The following table is a *suggested* payment schema. Participant and family will receive up to \$500 if they complete the entire study (subject to site IRB approval).

Screening	(Screening/Consent)	\$ 25.00
PSG	(Screen Research PSG (if needed))	\$100.00
Baseline	(Baseline Morning Testing)	\$100.00
Visit 2	(Month 3 Brief Follow-up)	\$ 50.00
Visit 5	(Month 7 Final End Point)	\$200.00

In addition, small material incentives (water bottles, night shirts with study logos, etc) also will be provided. Each site may make arrangements to reimburse families for costs, as needed, for transportation, parking, and other meals that would not be adequately compensated with the visit-specific reimbursement.

26. Appendices

- A. Visit Schedule
- B. Informed Consent Template / Assent
- C. Adverse Events
- D. NHLBI Data Sharing Policy
- E. References

Appendix A: CHAT Visit Schedule

Procedures and Assessments	Preliminary Screen Sleep Lab/Clinic		Confirm Final Eligibility		EAT Only	Visits Both Arms					WWSC Only
	ENT ¹ V1	PSG ² V2	Baseline V3	Randomize ⁷ V4 (not a visit) administrative procedure only	Surgery V5	Phone Contact V6	Clinic Visit (Brief) V7	Phone Contact V8	PSG V9	Clinic Visit (end of study) V10	ENT Re-Eval V11
Visit	Screen		Baseline	Day 0	EAT Only	Phone	Clinic	Phone	PSG	Clinic	WWSC Only
Time	Day -60 to -1			At baseline or w/in 48 hrs of baseline	M1 w/in 1-4 wks of randomization	M2	M3	M5	M6 ⁸	M7	M8 (w/in 1-4 wks of M7)
Preliminary Eligibility Review and/or Informed Consent	X	X									
ENT evaluation ¹	X										
Polysomnography (PSG) ²		X							X		
Randomize				X							
Surgery					X						
Re-evaluation for AT surgery [WWSC only]										WWSC - Remind family of scheduled ENT visit M8	X
PE			X							X	
Resting BP			X				X			X	
Anthropometry			X				X			X	
Fasting Blood (glucose, insulin, lipids, CRP) optional DNA ³			X							X	
Neuropsych (NP) Testing (Version set 1 or 2) ⁴			X ⁴							X ⁴	
Parent NP Questionnaires ⁵			X							X	
Review take home educational materials			X Healthy Life Style Packet				X PJ BEAR			X	
Dispense NSS ⁶			X				X				
Sleep/ Activity 5-day Log ⁸			X						Distribute 5 day sleep journal for return at M7	X return completed sleep journal	
Teacher Report Forms ⁹			X							X	
Adverse event inquiry		X	X		X	X	X	X	X	X	
Medication inquiry		X	X		X	X	X	X	X	X	

Appendix A: CHAT Visit Schedule

- 1 Existing ENT evaluations (within 90 days prior to randomization) can be utilized to establish preliminary eligibility for surgical candidacy. WWSC group will be re-evaluated at Month 8 (within 1-4 weeks of the M 7 visit).
- 2 An overnight PSG exam must be performed and approved by the SRC prior to randomization unless an existing PSG (done within previous 60 days prior to randomization) has been approved by SRC. Another PSG will be completed at Month 6 for those who are eligible and enrolled in the study.
- 3 Samples will be processed and stored locally for shipment to central repository on a monthly basis. Consent for genetic testing must be obtained.
- 4 Psychometrician assigns and documents NEPSY Version set (1 or 2). Same version set is used at Baseline and Month 7..
- 5 Psychometrician instructs parent who will complete in separate room.
- 6 Dispense NSS. Provide verbal and written instructions.
- 7 Not an actual visit. Listed in the database as Visit 4 for tracking purposes only. Randomization is an administrative procedure that can easily be completed at the end of the baseline visit before the family leaves the clinic (ideal). All eligibility requirements should be known by the time of the baseline visit except the DASII. Therefore, in most cases randomization can occur on the day of the baseline visit while the parent and child remain in the clinic, once the DAS II eligibility score is determined by the psychometrician. In the event that DAS II eligibility cannot be scored on the day of the baseline visit, the psychometrician has up to 48 hours to provide the unblinded coordinator with the results so that randomization can occur.

Note: Once the randomization assignment is known and consent reaffirmed with family:

EAT - schedule surgery to occur within 1-4 weeks from baseline/randomization.

WWSC - schedule re-evaluation with ENT at this time to occur 1-4 weeks after the month 7 visit.

- 8 **Baseline:** Recording of sleep habits and general activity will start the day of baseline visit (complete first page of the diary with parent as they recall the child's sleep pattern the night before baseline and instruct them to complete it for the next 4 nights and return in a self addressed stamped envelope).
- Month 6** – Distribute the 5 day sleep journal the night of the PSG for the parent to record child's sleep patterns for 5 nights (excluding the night of the PSG) and to return the completed diary at the Month 7 visit.
- 9 Authorization to Release Information Form must be signed and completed by the parent prior to Teacher notification. 1st month of school or summer; contact teacher of previous year.

INFORMED CONSENT TEMPLATE

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

P.I. Name and Department
Telephone Numbers(s)
Co-P.I. Name(s)
Day Telephone Number(s)
24-Hour Emergency Number
IRB # of protocol

STUDY TITLE:

A Randomized Controlled Study of Adenotonsillectomy for Childhood Sleep Apnea

Study Key Name: CHAT

Invitation to Participate

We invite your child to take part in this research study. This form is called a consent form. The information in this consent form will tell you about what will happen during the research study and the risks and possible benefits of taking part in this research study so that you can decide with confidence whether you want your child to participate. The form also includes other important information about the research study, including the health information we will collect. Please read this information carefully before deciding whether you want to take part. If there is anything you do not understand, please ask questions. Parents or legal guardians who are giving permission for a child, please note that the word “you” in this consent form refers to either you or your child.

Being in this research study is voluntary. You do not have to have your child take part in this study if you do not want to. If your child does take part in this study, he/she can leave the study at any time.

This study is sponsored by the National Center on Sleep Disorders Research a part of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). This study will be conducted at the following clinical centers representing the study organization:

1. Cincinnati Children’s HospitalCincinnati, OH
2. Children’s Hospital of PhiladelphiaPhiladelphia, PA
3. Rainbow Babies and Children’s Hospital.....Cleveland, OH
4. Cardinal Glennon Children’s Hospital St. Louis, MO
5. Montefiore Children’s Hospital New York, NY
6. Children’s Hospital of Boston Boston, MA

Overall, it is expected that 460 children will take part in this research study.

Appendix B: Informed Consent Template

Why is your child being asked to take part in this research study?

Your child is being invited to take part in this study because your child has enlarged tonsils and symptoms of sleep apnea, such as snoring. Sleep apnea is a condition diagnosed with an overnight sleep study that shows breathing pauses (also called “apneas”) during sleep.

The most common cause of SLEEP APNEA in children is enlarged tonsils and adenoids. Sleep Apnea can also be found in children who have a small breathing airway and normal tonsil size. Tonsils are glands located on both sides of the throat and adenoids are glands located in the back of the nose and throat.

SLEEP APNEA may cause health problems, such as poor growth, high blood pressure, behavioral problems and learning problems.

The usual treatment for children with SLEEP APNEA is surgery to remove the tonsils and adenoids. This treatment is called adenotonsillectomy surgery.

What is the purpose of this research study?

The purpose of this research study is to see if adenotonsillectomy surgery helps to reduce the sleep apnea and improve breathing during sleep. Another purpose of this research study is to find out if behavior, learning, blood sugar and blood pressure levels improve after adenotonsillectomy surgery. We also want to find out if children with sleep apnea who are overweight or of different ethnic groups are helped by the surgery.

We are doing this study because we do not know the best way to treat sleep apnea in children. Although adenotonsillectomy surgery is the usual treatment for sleep apnea in children, it has never been properly tested. For some children with sleep apnea, breathing during sleep may improve without having surgery though this has not been tested. We do not know how many children improve after surgery, and how many children continue to have problems.

How long will my child be in this research study?

This research study will last about four years. The length of time your child will take part in the research study will be one year.

What is involved in this research study?

This research study involves the following: At the start of the study, all children will be evaluated for sleep apnea and will be evaluated by an ear, nose, and throat doctor. One group of children will get surgery approximately one month after they are enrolled in the study. The other group will not get surgery in a month after they are enrolled, but will wait and be re-evaluated for surgery approximately seven months after they are enrolled in the study.

All children (in both groups) will be given information about good sleep and health habits. All children will be given a salt-water nose spray to be used at bedtime as needed. All children will have their medical history reviewed by a research doctor who may make recommendations for improving health.

This research study will require your child to have overnight sleep studies at a sleep center, blood tests, and clinic visits for physical and behavioral testing. There will also be scheduled phone contacts with you between the clinic visits. You will complete forms that ask questions about your child, and

Appendix B: Informed Consent Template

about your family medical history. Your child's schoolteacher will also be asked to complete a questionnaire about your child.

The following are the clinic visits, tests and procedures required for this study.

Screening Visit

At this first visit, we will see if your child is eligible to take part in this research study. Your child's medical chart and medical history will be reviewed. Information such as medications your child takes, past medical problems and past surgeries will be reviewed.

Your child will receive an examination by a doctor who specializes in ear, nose, and throat problems. This is called an ear, nose, and throat evaluation and requires the doctor to look inside your child's throat, ears, and nose with a small flashlight. This ear, nose, and throat evaluation may occur at the screening visit or may be scheduled as a separate visit at an Ear, Nose, and Throat Clinic. If your child has received an ear, nose, and throat evaluation within 3 months before entered into the study the results of that evaluation will be reviewed to see if your child is eligible to participate in the research study.

Your child will also be scheduled for an overnight sleep study at a Sleep Center. If your child has had an overnight sleep study less than two months before being entered into the study then the results of that sleep study will be evaluated to see if your child is eligible to participate in the research study.

Sleep Study Visit

A sleep study is a routine clinical test that will tell us if your child has sleep apnea or not. The sleep study is done overnight at the sleep center. Before going to sleep for the night at the sleep center, a number of small patches will be placed on the skin of your child's head, face, chest and legs and a patch will be taped around your child's finger or toe. These patches will be connected by wires to machines in a separate room where your child's breathing, heart rate, leg movements, and sleep will be monitored. Your child will wear stretchy belts that are placed around the chest and belly to measure breathing. Small plastic tubes will be placed in the nose to measure your child's breathing. A video recording of your child is made while they are sleeping to monitor the testing. You will sleep in the same room as your child during the testing.

In order to be eligible for the research study, the results of your child's sleep study must be abnormal and show that your child has sleep apnea. If the sleep study is very abnormal and shows a severe condition of sleep apnea, your child will not be enrolled in the research study as we think it may not be safe to wait for surgery if a child has a severe condition of sleep apnea.

Randomization

If your child is eligible to be in the research study, they will be randomly assigned to one of the two treatment groups talked about below. "Randomly Assigned" means being put into a group by chance. It is like flipping a coin. Your child will have an equal chance of being in either group. A computer will choose which group your child will be in. The main research study doctor will not know which group your child is in.

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One treatment group will have early adenotonsillectomy surgery that will be scheduled within one month after being enrolled in the study. This is called the *Early Adenotonsillectomy Surgery* group.

The second treatment group will be re-evaluated for surgery by the ear, nose, and throat doctor about 7 months after being enrolled in the study. If the ear, nose, and throat doctor finds that surgery is needed, then surgery will be scheduled by the ENT's office to occur within one month of the 7month visit. This is called the *Watchful Waiting with Supportive Care* group.

Children in both groups will be given sleep and health information, a salt-water nose spray to use as needed at night, and will have their medical history reviewed to make sure all medical problems are well addressed.

Baseline Visit

During this visit, you will have a number of tests done. These tests will take about 4 hours and must be done in the morning. There will be breaks scheduled during the tests so that your child doesn't get tired. Your child cannot eat for 10 hours before the blood test, but will be able to eat breakfast as soon as the blood sample is taken. The following are the tests that will be done:

1. Blood will be taken from your child to test your child's blood sugar, insulin, lipids (fat and cholesterol) and C-reactive protein (a test of inflammation). This requires that a vein in your child's arm to be pricked with a sterile needle and approximately 2 tablespoons of blood will be collected into a tube. Because a needle stick can be painful for your child, the doctor may order a medicine cream that is used to numb the skin so that your child will not feel the needle as it goes in. Before your child is scheduled for the blood test, you will receive instructions on how to apply the cream to your child's skin.

We would like to store a sample of this blood for future genetic testing to help us research the cause of sleep apnea and the health problems related to it. You will be asked to sign a separate consent form for collecting and storing a genetic blood sample from your child.

2. A brief physical examination will be done. This will include height, weight, blood pressure, and measurements of the neck, waist and hips. A research doctor will also look into your child's mouth with a flashlight, and do a brief physical examination as is usually done in a doctor's office.
3. Behavior and learning tests will be done. A trained research assistant will give your child tests that examine memory, intelligence, behavior and mood. You will be in a different room and will fill out questionnaires about your child's health and behavior while your child is being tested.
4. A Teacher Questionnaire. With your permission, we will mail to your child's teacher two brief questionnaires to fill out. These are questions about how your child is doing in school. We will ask you to tell us the name of the teacher that knows your child best, and to sign a form giving the teacher permission to fill out the questionnaires. We will then mail the teacher a letter. If you prefer, you can give the teacher the letter yourself.
5. Sleep diary. You will be asked to fill out a 5-day sleep diary showing what time your child gets up in the morning and what time your child goes to sleep at night and some general questions about beverages you child drinks and your child's activity level.

Appendix B: Informed Consent Template

Treatment

If your child is randomized to the Early Adenotonsillectomy Surgery group, your child will receive adenotonsillectomy surgery within one month of completing the baseline tests. You will be given a supply of salt water nasal spray for your child to use at bedtime if needed, to help with nasal dryness. You will be given information about good sleep habits. Your child's medical history will be reviewed by the research doctor who may make recommendations to you or your child's other doctors on ways to improve your child's health

If your child is randomized to the Watchful Waiting with Supportive Care group, your child will be re-evaluated for surgery by the ear, nose, and throat doctor about 7 months after completing the baseline tests. If the ear, nose, and throat doctor finds that surgery is needed, it will be scheduled. You will be given a supply of salt water nasal spray for your child to use at bedtime if needed, to help with nasal dryness. You will be given information about good sleep habits. Your child's medical history will be reviewed by the research doctor who may make recommendations to you or your child's other doctors on ways to improve your child's health.

As a measure of surgical quality control in this research study, photographs of the inside of the throat will be taken on every 10th child. Your child may be selected. A photograph of the inside of the throat will be taken before and after the tonsils and adenoids are removed. These photographs will add less than a minute to the time for surgery. Your child will not be identified as the photos are only of the inside of the mouth.

Follow-up phone calls

You will get a phone call from the study staff 2 times during the 7 month study period to see how things are going and whether there are any problems (for example, questions about new illnesses, health or behavioral concerns, unscheduled doctor visits, medications).

3-Month Clinic Visit

This is a research clinic visit that occurs three months after enrollment in the study. Your child will have height, weight and blood pressure measured again at this visit. This visit will last about 30 minutes.

6-Month Sleep Study

Your child will have another overnight sleep study at the sleep center 6 months after entering the study. The same sleep study procedures will be done just like they were done for the first sleep study. Also like the first sleep study, you will sleep in the same room as your child during the testing. You will also be given another sleep journal to record your child's sleep patterns again for 5 nights. The study staff will ask you to return the completed journal at the 7 month visit.

7-Month Clinic Visit and Testing

Your child will return to the research clinic where all the tests that were given at the baseline visit will be repeated. (Please see baseline visit on pages 4 & 5 for details of the tests). These tests will take about 4 hours all together, and must be done in the morning.

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The tests include the blood sample (your child cannot eat for 12 hours before the blood sample is taken), physical exam, behavior and learning tests, teacher questionnaire., and sleep diary.

If your child is in the Watch Waiting with Supportive Care group, they will be seen again by the ear, nose, and throat doctor who will decide whether your child should have adenotonsillectomy surgery. If surgery is recommended, then the surgery will be scheduled to be done within approximately one month of this visit.

What are the risks of taking part in this research study?

Taking part in a research study involves risks or “side effects.” You should talk about these risks or side effects with the study doctor, the ear, nose, and throat doctor, or your child’s regular doctor. There may be risks or side effects we do not know about yet.

While in this study, your child is at risk for the following side effects:

Side Effects of later or delayed surgical treatment of sleep apnea:

The possible side effects of untreated sleep apnea may include behavioral, learning, blood pressure, blood sugar and growth problems. For children randomized to *the Watchful Waiting with Supportive Care* group, we believe the 7-month wait or delay period before surgery is within a safe range and waiting for surgery is not a danger to your child. We will closely follow your child’s condition during this period. If your child develops symptoms of severe sleep apnea during this wait period, immediate surgical treatment will be needed. If your child develops new health or behavior problems during the study like high blood pressure, prompt surgery also may be recommended.

Side Effects of adenotonsillectomy surgery and general anesthesia:

Common side effects of adenotonsillectomy surgery are temporary sore throat with painful swallowing and minimal blood loss that can be expected to last up to 7-10 days after surgery. Less common side effects can occur such as dehydration, a larger than expected blood loss, infection, trauma or burns to teeth or the throat, temporary difficulty with swallowing or speech or regrowth of tonsil or adenoid tissue. These problems may require blood transfusions, speech therapy or additional surgery. Very rare complications of surgery include scarring of the airway, serious infections, and death.

Adenotonsillectomy surgery is done under general anesthesia. General anesthesia affects the entire body and makes the person unconscious. Although general anesthesia involves some risk, major side effects and complications from anesthesia are uncommon.

Common side effects of general anesthesia include nausea, vomiting, and 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.

Before undergoing surgery, the surgeon and anesthesiologist will meet with you to discuss any questions you or your child may have about surgery and anesthesia. Additional details related to adenotonsillectomy surgery and general anesthesia will be discussed at this time. You will be asked to sign a separate surgical consent form before your child receives surgery.

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Side Effects of Blood Tests: Taking blood may cause some discomfort or pain, bleeding or bruising at the spot where the needle pokes through the skin. Rare Side Effects: Taking blood may cause nausea, lightheadedness, or fainting or infection at the area where blood is taken.

Side Effects of Numbing Cream: The medicine cream used to numb the skin before the blood test may cause some redness, swelling, itching, or rash on the skin where the medicine is applied.

Side Effects of Sleep study: The sleep patches for the overnight sleep study are attached with paste and tape and may cause some irritation of the skin. Sleeping overnight away from home can be distressing for some children, however, you or another family member will sleep in the same room with your child during the sleep study.

Side Effects of behavior and learning tests: Some children may find taking the behavior and learning tests to be mildly stressful. If a particular question makes your child uncomfortable, they will not be required to answer the question.

Are there any benefits to taking part in this research study?

There may or may not be a direct medical benefit to your child if he/she takes part in this research study. Your child may be identified during this study as having a medical problem you did not know about like high blood pressure, diabetes, or high cholesterol, which would benefit from early treatment. At the end of the study, you will also receive the results of your child's behavior and learning tests, and be referred for further evaluation if these tests are abnormal. In the unlikely event that the behavior tests show severe depression or suicidal intent, your family will be notified and you will be referred for further help.

Do you need to give your consent to get treatment?

Yes, you need to give consent for your child to be in this research study. If you do not give consent, your child can still get clinical treatment without being in this research study.

What happens if you decide not to have your child take part in this research study?

If you decide not to have your child take part in this research study, your child's current and future medical care at *(Insert name of Institution)* will not be affected and your child will receive the same standard of health care given for sleep apnea.

What if you want to have your child leave the research study after he/she begins?

Being in this research study is voluntary. You may choose to have your child leave the study at any time.

This research study is expected to end after all participants have completed all visits, and all information has been collected. The study doctor may have your child leave the study at any time without your consent for the following reasons:

- Your child's condition worsens
- Your child cannot meet all the requirements of the research study
- You decide to take back the permission you gave for us to collect, use or share your child's health information
- New information suggests that taking part in the research study may not be in your child's best interests
- The research study is stopped by the study doctor or the study sponsor

Appendix B: Informed Consent Template

Will confidential health information be collected as part of this study?

Yes. We need to collect your health information to conduct this study and we will keep it confidential as required by law. Every effort will be made to keep your child's health information private. Your child's study information will be given a unique code. Your child will never be tracked through the study by name, medical record number, or other personal identifiers. The key to this unique code will be kept in a locked file or a password-protected computer file in the study team's locked office.

The University of Pennsylvania serves as the Data Coordinating Center for this research study. All the study information from all the research centers, after being stripped of your child's identifying information, will be stored in secure electronic files at the University of Pennsylvania. All study data will be sent to the Data Coordinating Center by secured internet connection. Quality control measures for the sleep and blood pressure studies will be directed by Harvard. . Quality control measures for surgery, and the behavioral and learning studies will be directed by the University of Michigan. Only authorized members of the research study will have permission to see the study data. Authorized representatives of the Sponsor, the National Center on Sleep Disorders Research a part of the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), the Institutional Review Board (*insert name of institution*), may have access to an may copy medical or research records that identify your child by name. This step is necessary to insure the accuracy of the research findings and your safety and welfare.

The results of this study may be shown at meetings or published in journals so other doctors and health professionals know about the study. Your child will not be identified by name or other personal identifier in any publication or presentation about the study.

The information collected about your child as part of this study will be retained for at least seven (7) years or until the study is completed, whichever is longer. At that time, the research information will either be destroyed or all the information that identifies your child will be removed from the study results and the key destroyed.

Use of your child's information in future studies

Your child's information may be useful for other studies. We can only use your child's information again if special committees, called the Institutional Review Boards, let us. These committees may want us to talk to you again before we do another study using your child's information, or the committees may also let us do research without talking to you again if we keep your child's health information private. You may also tell us that you do not want us to use your child's information in future studies.

What happens to the health information if you want your child to leave the study?

You do not have to have your child take part in this study if you do not want to. You can have your child leave the study at any time or ask that your child's health information not be used. If you ask that we no longer collect your child's health information, then your child will have to leave the study.

If you chose to have your child leave the study, but will let the researchers use or share your child's personal health information, you will be asked to fill out a form, called the "Withdrawal from Study" form.

If you do not want us to collect, use or share your health information anymore, you must send a letter to the study doctor. In the letter, you must say you changed your mind and that you will not allow us to use and share your child's health information anymore. We will then ask you to fill out a form, called a "Withdrawal of Study Participation and Consent/Authorization" form.

Appendix B: Informed Consent Template

Even if you take back your permission for us to use your child's information, we may still use the information about your child that we collected before you left the study. We do this because we need to know what happens to everyone who starts a research study.

What will we do with the blood we collect from your child?

As part of the study, we will collect blood samples. Information that can identify your child will not be placed on the samples. The blood samples will be shipped to the University of Vermont Research Biochemistry Laboratory, where they will be analyzed and permanently stored.

If you have your child leave the study, you can ask that your child's blood samples be destroyed.

What will it cost you to have your child participate?

The cost for the following research procedures will be paid for by the research study funds: Physical examinations, blood tests, behavioral and learning tests.

The cost of the first research sleep study to determine if your child meets criteria to participate in this study will be paid for by the research study *if your child's doctor did not order a sleep study and you have consented to participate in this study*

However, if your child's doctor has already ordered a sleep study as part of routine care for your child, then the cost of clinical care sleep study that your doctor has ordered is the responsibility of you and your insurance company.

The costs of the second research sleep study will be paid for by the research study funds.

Costs related to surgery: You and/or your insurance company, Medicare or Medicaid will be responsible for the costs of the adenotonsillectomy surgery that your child receives during this study. Since surgery is the usual treatment for sleep apnea, these are costs that are considered medically reasonable and necessary and will be part of the care your child receives if they do not take part in this study.

Will you be paid for taking part in this research study?

For taking part in this research study, you will be paid (*Customize per clinical center - specific participant payment information should be itemized*)

Who is funding this research study?

This research study is supported by grants from the National Heart Lung and Blood Institute, and the General Clinical Research Center, which are part of the National Institutes of Health. The National Institutes of Health is a part of the federal government. It conducts and funds medical research. The results of the study will be reported to the National Institutes of Health.

What if you have questions about the study?

The (*Insert your Institution's name*) has a committee called the Institutional Review Board. It is their responsibility to make sure that the research being conducted is safe and that people in the study are informed about risks and benefits of the research study. If you would like more information or have

Appendix B: Informed Consent Template

questions about your child's rights as a research subject, you can contact the Office of Regulatory Affairs
(insert appropriate information for your clinical site IRB)

What happens if your child is injured during the study?

Your child will not get free care, payment or special services from (insert name of institution) or the study sponsor if your child is injured while taking part in this study. Doctors at these hospitals can arrange for emergency medical care if your child is hurt or gets sick from something that is done as part of this study. You will not pay for this emergency care if your injury is caused by the experimental part of this study. Otherwise, treatment for your injuries will be paid for the same way you usually pay (for example, through your insurance)

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to have your child participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your child's participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

Printed Name of Participant

Parent or Legal Guardian signature

Date

Relationship to Child

Signature of Person Obtaining Consent

Date

Printed Name, Person Obtaining Consent

(Must be study investigator or individual who has been designated in the Checklist to obtain consent.)

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

(Affirming subject eligibility for the study and that informed consent has been obtained.)

Appendix B: Informed Consent Template

SEPARATE FORM: TEMPLATE FOR GENETIC TESTING

SEPARATE SIGNATURE REQUIREMENTS FOR OPTIONAL GENETIC BLOOD SAMPLE

PROCEDURE FOR GENETIC SAMPLE: You will be asked to allow genetic testing on a blood sample that will be collected from your child and stored as part of the Childhood Adenotonsillectomy study. This test does not require a separate blood draw.

A part of the blood sample holds genetic information. If you agree, some of your child's blood sample will be stored separately for future genetic analyses. Your child's genetic sample will be stored at a central laboratory under a code number. All results of genetic testing will be stored under a code number without personal identifiers in a secure, password-protected database. The researchers who view this database will not have access to your name or identifying information. You will not be informed of any of the results of the genetic testing on your child's blood. The results will not be placed in your child's medical record. Your child's genetic sample will be used to study the causes of sleep apnea and other conditions that may be related to sleep apnea such as high blood pressure and metabolic problems. The genetic blood sample will be stored separately for future genetic analyses. Or, to provide a larger amount of the genetic blood sample for analysis in the future, we can store your blood in a way that that allows blood cells to live and grow indefinitely. This is called creating a cell line from your blood cells. The samples will be kept for up to 50 years or through the end of the study.

RISKS: The kind of genetic information being analyzed in the Childhood Adenotonsillectomy Study is not likely to have any direct effect on your child's health. There is the unlikely risk that if people other than the researchers got your genetic information they could misuse it. The chance of this ever happening to you is very small.

The risks of the blood draw are the same as listed in the RISKS section of the consent for participation in the study.

BENEFITS: There is no direct benefit to your child's participating in the genetic part of the Childhood Adenotonsillectomy study. You will not be informed of any results of the genetic testing on your child's blood. However, your contributions may benefit medical practice through knowledge gained.

CONFIDENTIALITY: Results of genetic testing will be kept private. The genetic sample will be stored at a central repository at the University of Vermont with a code number by study, under the direction of the National Institutes of Health and National Heart, Lung, and Blood Institute (NHLBI) for future investigations. These future investigations may include medical research projects for other medical conditions. The National Heart, Lung, and Blood Institute repository has been established to store samples from many research projects around the country in order to conduct large research studies. Your child's name or other information that could identify your child will not appear on the genetic samples or results. Only certain study Investigators who are working directly with the genetic samples will have the master code that links your child's name with the code number. This master code will be kept in a secure location.

Researchers who plan to use your sample for future scientific study will have to request and receive all of the necessary approvals from the National Heart, Lung, and Blood Institute and Childhood Adenotonsillectomy Study investigators before using your sample. Samples will only be released to scientists who are qualified and prepared to conduct a research study.

ALTERNATIVES: Your alternative is not to participate in this genetic testing.

VOLUNTARY CONSENT: Your child's participation in the genetic testing part of this research study is voluntary. You may choose not to allow your child to join in this part of the study even if you decide to participate in the Childhood Adenotonsillectomy study previously described in this informed consent form.

Appendix B: Informed Consent Template

If you do decide that your child can be part of this genetic testing, but later you change your mind, you must notify the Investigator listed on the front of this informed consent form in writing so that no additional genetic testing will be performed.

You may also decide to participate in some level of genetic testing but not another, as specified in the choices below.

CONSENT FOR GENETIC RESEARCH

Instructions: For each question, please **CIRCLE "YES" or "NO"** and write your initials and today's date in each row where indicated. Please circle either **"YES"** or **"NO"** for the following question.

- | | | | <u>Initials</u> | <u>Date</u> |
|---|------------|-----------|-----------------|-------------|
| 1. I give my permission to genetically test my child's blood samples | YES | NO | _____ | _____ |
| 2. I give my permission to genetically test my child's blood for the main goals of this study: learning the cause of Childhood Sleep Apnea and for health conditions related to sleep apnea | YES | NO | _____ | _____ |
| 3. I give permission to genetically test my child's blood for other health conditions. | YES | NO | _____ | _____ |

SIGNATURES:

I have had the optional genetic testing section of this research study explained to me. I have read the informed consent document. I have had the chance to ask questions. They have been answered to my satisfaction.

My signature below means that I voluntarily agree to have my child participate in the genetic testing part of the research study. I have chosen the types of testing I have agreed to. I will be given a copy of this form for my records.

_____	_____	_____
Date	Signature of Participant (or Legally Authorized Representative – note relationship to participant)	Printed Name

_____	_____	_____
Date	Signature of Witness (Only required if the participant can not read this consent)	Printed Name

I have discussed the optional genetic testing part of the research study with the participant or his/her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed the participant of the nature of this study and its possible benefits and risks.

_____	_____	_____
Date	Signature of Person Obtaining Consent	Printed Name

CHILDHOOD ADENOTONSILLECTOMY (CHAT) STUDY

There might be words you do not know when you are hearing or reading about the study. Please ask the study staff or study doctor to tell you more about anything you do not understand.

What is a research study?

A research study is a way to learn new things. Kids do not need to be in a research study if they do not want to.

Why are you being asked to be part of this research study?

You have some trouble breathing at night. This is called “Sleep Apnea.” Your doctor thinks that surgery can help you. More than 400 kids will be in the study.

What is this study about?

This study will tell us if surgery helps you. The study will also tell us if the surgery helps you act and feel better in the day.

If you join the study, what will happen to you?

Some kids will have surgery at the start of the study. Other kids will have surgery later. You will have the same chance of surgery when the study starts or later on.

- The study staff can tell you more about what happens at each of the study visits.
- There are 4 study visits in one year. During the study, each of these things will happen:
 - The study doctor will do a check-up.
 - The study nurse will check how you are growing.
 - You will stay at the hospital at night 1 or 2 times. Each time you will have a sleep test.
 - You will answer questions about how you feel. You will also have thinking tests.
 - You will have a blood test at two times.

Some of the visits may take a long time. You can take a break so you do not get tired.

If you do not want to do any of these things, you can say you do not want to be in the study.

Will any part of the study hurt?

- The sleep test uses stickers that are put on your skin. The stickers do not hurt when they come off.
- You will feel a “squeeze” around your arm when we check your blood pressure.
- We will ask some questions about your feelings. If a question makes you feel bad, you do not have to answer it.
- You will feel a poke with a needle for the blood test. We will put special numbing cream on your skin for the blood test. Even though you have special cream on your skin, you will feel a pinch from the needle. No one will make you have the blood test.

Appendix B: Assent Template

Will the study help you?

The study may or may not help you.

Will the study help others?

This study might find out things that will help other kids like you.

Do your parents know about this study?

Your parents know and said it was OK to talk to you. You can talk this over with them.

Who will see the information collected about you?

The people doing the study will see. We might write about what we learn in books. We will not use your name.

What do you get for being in the study?

You and your parents will get some money for each part of the study you do. Ask your parent to tell you more.

Do you have to be in the study?

You do not have to be in the study if you do not want to. No one will be upset. You just have to tell us.

What if I have any questions?

The study staff will answer all your questions. Please ask about us about anything. If you have a question later, you or your family can call the study doctor.

You can also take more time to think about being in the study. You can talk some more with your parents about being in the study.

What choices do you have if you say no to this study?

Your doctor will take care of you without being in this study.

Other information about the study:

If you decide to be in the study, please write your name below.

You can change your mind and stop being part of it at any time. All you have to do is tell the person in charge.

Appendix B: Assent Template

You will be given a copy of this paper to keep.

Write your name

Witness

Date

If the child is not able to read the assent form:

Verbal assent was obtained using the content in the assent form.

I have discussed this clinical research study with _____, using language, which is understandable and appropriate. I believe I have fully informed him/her of the nature of the study and its possible risks and benefits. I believe the participant understood this explanation and assented to participate in this study.

Research Staff Member

Date

C-1: Glossary for Key Terms

Adverse event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

Possibly related to the research: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)).

Serious adverse event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- (1) results in death;
- (2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- (3) requires inpatient hospitalization or prolongation of existing hospitalization;
- (4) results in a persistent or significant disability/incapacity;
- (5) results in a congenital anomaly/birth defect; or
- (6) any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse). Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).

Treatment Failure: is generally defined as a condition or situation that is observed during either routine interim follow-up phone calls or clinical visits (interim assessments specifically address these conditions, including questions and direct monitoring of weight and blood pressure at the 3 month visit) or as a result of study contact by the participant's family or physician (refer to section 16 for specific conditions). Conditions that may require additional/alternative therapies that may or may not be exclusionary criteria and are designed to minimize the potential risks to participant's safety:

- 1) Child's physician has identified a change in signs or symptoms that in his/her opinion warrant alternative treatment for OSA. Examples of such changes in clinical status include:
 - new academic or behavioral problems resulting in a recommendation for grade retention
 - special education
 - counseling or placement on medications for behavior, or emotional problems
 - new medical problems including 3-5 below
- 2) 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 chart

documentation of 3 culture positive infections will be 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 RC and paid for by the study.

- 3) New clinical diagnosis of cor pulmonale
- 4) Development of “failure to thrive” defined by weight loss during the course of study follow-up characterized by:
 - i. Weight falling below the 3rd percentile for age and gender **OR**
 - ii. Weight falling by two or more major isobars on the weight for age CDC percentile charts (<http://www.cdc.gov/growthcharts> **AND**
 - iii. The weight loss is not better explained by either an intentional weight loss (as part of healthy life style changes) or a transient loss related to an intercurrent acute illness such as viral gastroenteritis.
- 5) New onset of Stage 2 hypertension that is not better explained by another medical condition (for example, nephrotic syndrome).
- 6) New-onset hypersomnolence defined as reports of falling asleep on average > 3 times per week at school (not planned naps) despite spending adequate time in bed overnight (at least 10 hrs per night) that is not better explained by other factors unrelated to OSA (for example, intercurrent use of a new medication such as a sedating antihistamine). *These criteria only applies to children attending school.*

Note: this definition excludes children whose baseline BMI is $\geq 85\%$ for age and gender.

Treatment Failure Defined by Arm

Those conditions that may require alternative therapy during the 7 month study will be classified as treatment failure (in addition to those listed above) are described below:

Note: If alternative treatments are required, regardless of treatment arm assignment, the participant will remain in the study and followed until all visits and procedures have been completed through the 7 month trial period.

Early Adenotonsillectomy (EAT)

- Initiation of Continuous Positive Airway Pressure (CPAP) after AT surgery.
- Additional AT surgery, as clinical indicated.

Watchful Waiting Supportive Care (WWSC)

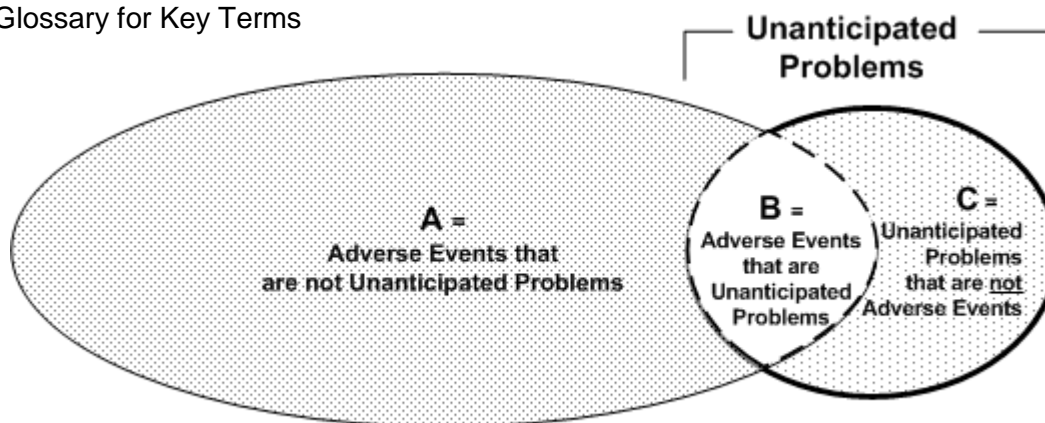
- Cross over to AT surgery for any of the reasons listed above.
- Initiation of Continuous Positive Airway Pressure (CPAP).

Parent/legal guardian (s) who decide that they no longer want to wait until the 7 month primary end point visit 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.

Unanticipated problem involving risks to subjects or others: Any incident, experience, or outcome that meets all of the following criteria:

- (1) 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;
- (2) related or possibly related to a subject's participation in the research; and
- (3) 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.

C-1 Glossary for Key Terms



Under 45 CFR part 46: Do not report A; Report B and C.

The diagram illustrates three key points:

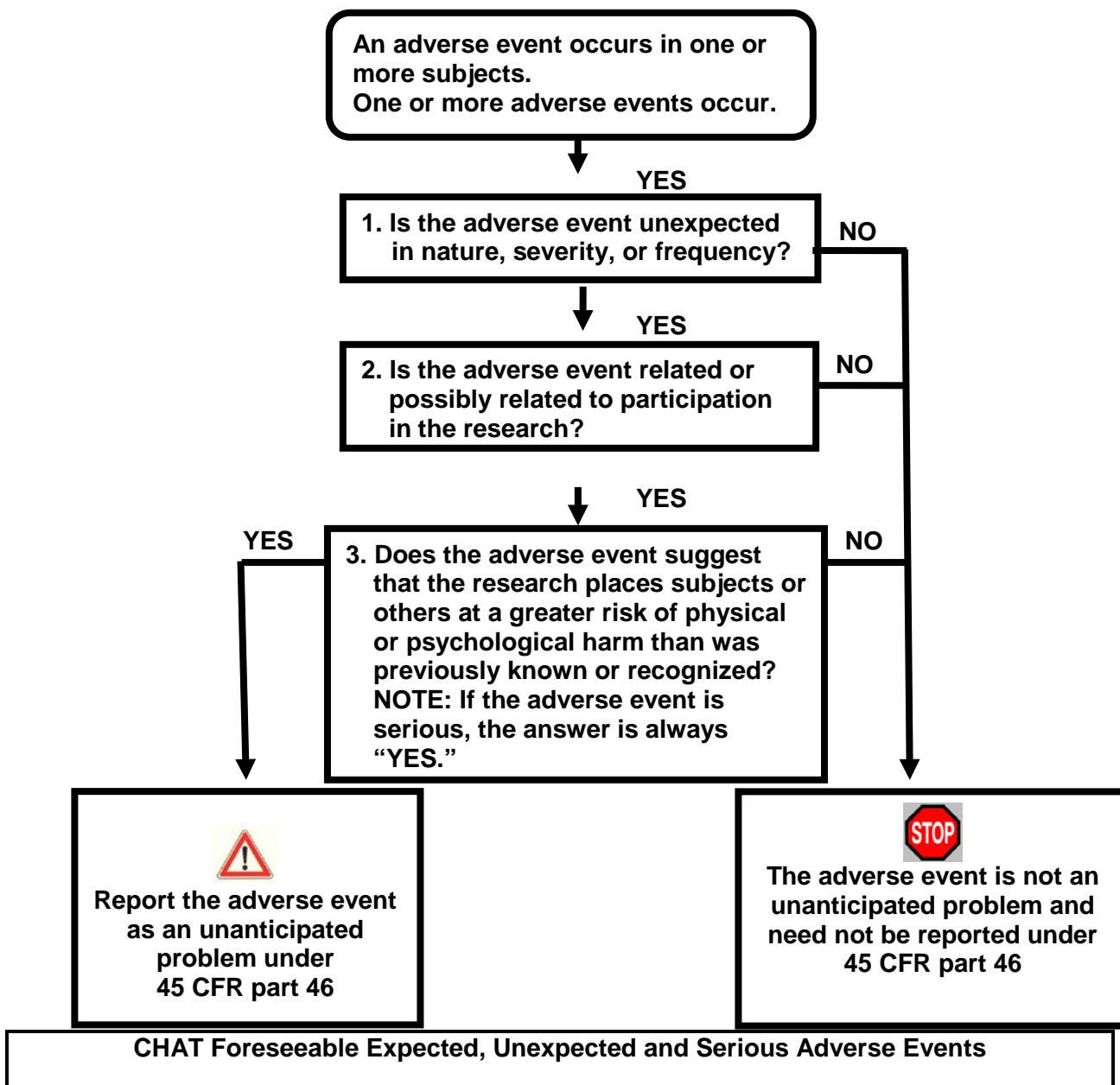
- The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).
- A small proportion of adverse events are unanticipated problems (area B).
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).
- To determine whether an adverse event is an unanticipated problem, the following questions should be asked:
 - Is the adverse event unexpected?
 - Is the adverse event related or possibly related to participation in the research?
 - Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is yes, then the adverse event is an unanticipated problem and must be reported to appropriate entities under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5)

Unexpected adverse event: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event (Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).

C-2: Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem



Category	Associated with PSG	Associated with AT	Associated with Phlebotomy	Other
Expected Adverse Events	Skin redness from removal of adhesives	Post-op sore throat < 21 days	Temporary Pain	Sneezing from nasal spray
	Temporary depigmentation under area of sensor attachment	Post-op hoarseness and difficulty swallowing < 21 days	Fainting without injury	Anxiety surrounding testing protocol
	Poor sleep during PSG	Intra-operative blood loss < 250 cc and/or post-op blood tinged oral or nasal secretions <i>for</i> < 72 hours		Nasal bleeding (small, temporarily associated with nasal spray)
		Velopharyngeal Insufficiency (nasal regurgitation or hypernasality) lasting < 2 months and not requiring specific evaluation or intervention		
Unexpected Adverse Events	Blistering of skin from chemical, thermal, or electrical contact requiring no treatment	Allergic reaction to medications requiring urgent physician evaluation or treatment or ER evaluation		Asthma exacerbation requiring oral steroid use or ER visit
	Bruise or cut from fall or hitting side rails during sleep requiring treatment	Pain or Odyngophagia associated with dehydration requiring urgent evaluation by physician or IV hydration	Phlebitis not requiring hospitalization	Nasal/sinus infection requiring medication
	Headache/nasal stuffiness or wheezing from adhesive fumes	Blood loss requiring urgent evaluation by physician or ER		Disclosure of PHI
		Trauma or burns to teeth or soft tissue requiring dental procedure or medical treatment, but not operative repair or hospitalization		Stage 2 hypertension*
		Velopharyngeal Insufficiency (nasal regurgitation or hypernasality) lasting > 2 months and not requiring specific evaluation or intervention.		Acute otitis, pharyngitis or sinusitis requiring medication

Appendix C-3 Foreseeable Adverse Event Table

CHAT Foreseeable Expected, Unexpected and Serious Adverse Events				
Unexpected Adverse Events, continued	Associated with PSG	Associated with AT	Associated with Phlebotomy	Other
		Post op infection		Injuries requiring ER visit
Serious Adverse Events	Blistering of skin from chemical, thermal, or electrical contact requiring hospitalization	Blood loss requiring transfusion, hospitalization or surgical procedure,	Embolus	Hospitalization <i>other than</i> AT r/t to the study, elective surgery or treatment of preexisting medical condition
	Fall from bed requiring hospitalization		Phlebitis requiring hospitalization	Death
		Intra or post-operative complications including breathing difficulties requiring prolonged intubation or unexpected ICU admission, atlanto-axial subluxation with neurological deficit, foreign body aspiration, airway fire;	Infection requiring hospitalization	
			Fainting with injury requiring hospitalization	
		Dehydration requiring rehospitalization		
		Velopharyngeal insufficiency requiring speech therapy or surgery		
		Nasopharyngeal scarring or stenosis requiring surgery		
		carotid pseudoaneurysm, cervical osteomyelitis, refractory torticollis		
		Death		

Table C-4: Grading Scale

Severity Grade	Description
1	Mild. Awareness of sign, symptom, or event, but easily tolerated; does not interfere with usual daily activities or tasks.
2	Moderate. Discomfort enough to cause interference with usual daily activity; may warrant therapeutic intervention.
3	Severe. Incapacitating; inability to perform usual activities and daily tasks; significantly affects clinical status; requires therapeutic intervention.
4	Life-threatening. Adverse event is life-threatening.
5	Fatal. Adverse event causes death.

Each event will be graded by the site PI as to its severity utilizing the following criteria:

Continued next page

C-5 Adverse Events Relationship to Study Definitions

Study Related Adverse Events: Each event will be determined by the PI at each site as to its relationship to the study intervention using the following criteria: 1) unrelated; 2) possibly related; 3) probably related; 4) definitely related. The PI will choose the category that overall best “fits” the relationship between the adverse event and the study intervention and record the evaluation on the AE case report form, if necessary. The terms used to describe the adverse event relationship to study treatment are listed in Table C5 below:

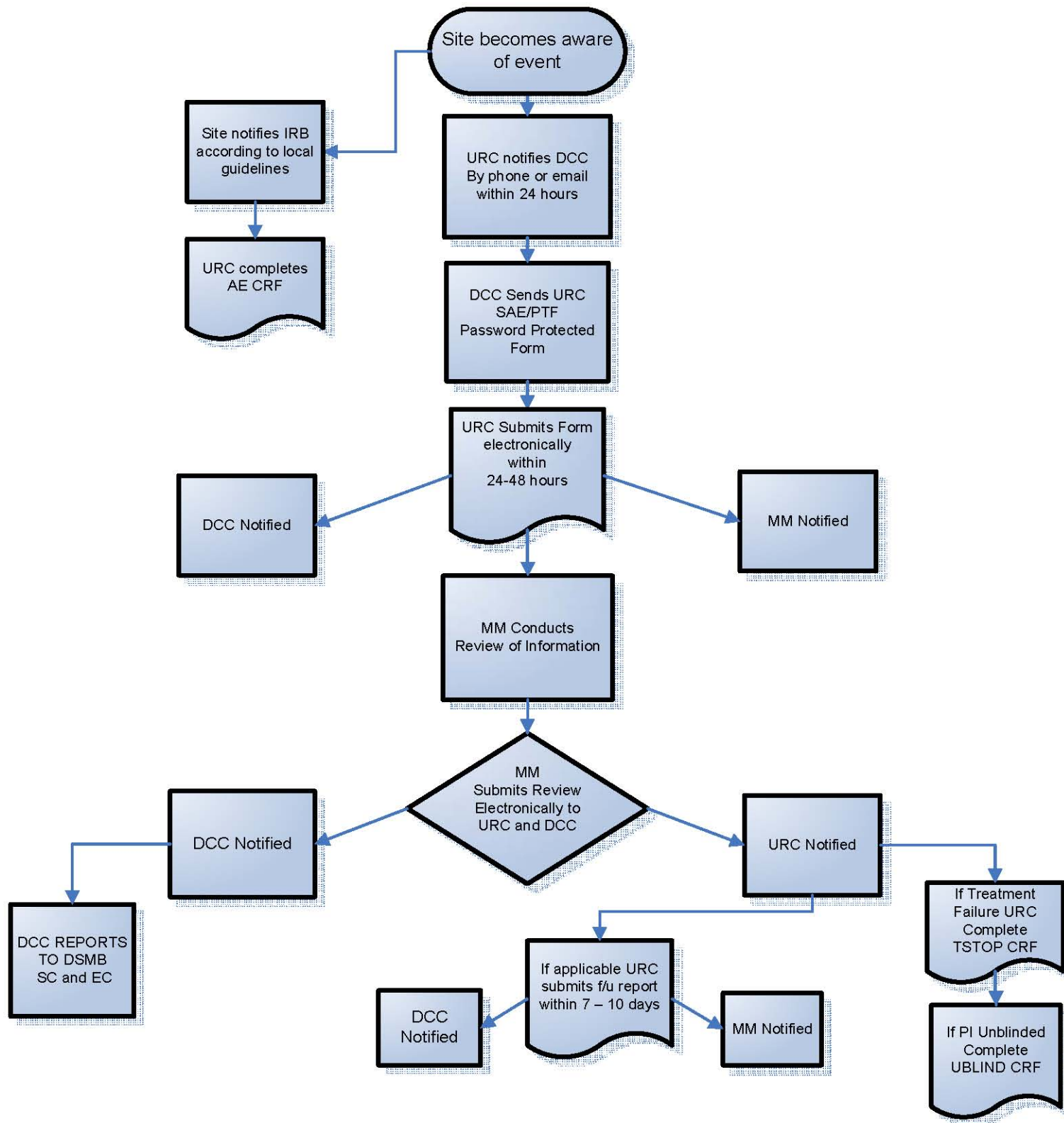
Table C-5: Relationship to Study Treatment

The following provides guidelines to making these determinations:

Relationship to Study	Grade	Description
Unrelated	1	<ul style="list-style-type: none"> No temporal association to study testing. An alternate etiology has been established. The event does not follow the known pattern of response to study test.
Possibly related	2	<ul style="list-style-type: none"> Reasonable temporal relationship to study test. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study test <u>or</u> as yet unknown pattern of response.
Probably related	3	<ul style="list-style-type: none"> There is a reasonable temporal relationship to the study test. Event could readily be produced by clinical state, environmental or other Interventions. The event does not follow the known pattern of response to study test.
Definitely related	4	<ul style="list-style-type: none"> There is a reasonable temporal relationship to the study test. The event is not readily produced by clinical state, environmental, or other interventions. The event follows a known pattern of response to the study test.

Note: Detailed instructions on AE case report form completion, relationship to study treatment, action taken, and seriousness of the event are listed in the Manual of Procedures.

CHAT Serious Adverse Event/ Potential Treatment Failure Reporting Process



Legend	
AE	Adverse Event
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EC	Executive Committee
IRB	Institutional Review Board
MM	Medical Monitor
PI	Principal Investigator
PTF	Potential Treatment Failure
SAE	Serious Adverse Event
SC	Steering Committee
URC	Unblinded Research Coordinator

Appendix D: NHLBI Data Sharing Policy

Department of Health and Human Services • National Institutes of Health

National Heart Lung and Blood Institute

Information for Researchers:

I. Introduction

II. Definitions

III. Data Set Requests

A. Responsibilities of Investigators seeking Access to Study Data

B. Responsibilities of Study Investigators in Preparing Data Sets

1. Documentation
2. Data Storage and Format
3. Content of Limited Access Data
4. Timing of Release of Limited Access Data

IV. Procedures for Protection of Privacy for Limited Access Data Sets

A. Institute Review and Approval of Limited Access Preparation

B. Guidelines for Limited Access Preparation

Note that the following policy is an update from the 10/25/2002 policy available at:
<http://www.nhlbi.nih.gov/resources/deca/policy.htm>.

For contract-supported clinical trials and epidemiology studies: Requirements for preparation of limited access data sets have been modified to shorten the timeline and expand the data to be included, as described below. These changes will be effective with contracts awarded on or after October 1, 2005.

For grant-supported new and competing applications for selected epidemiology studies and clinical trials: Applications received on or after October 1, 2005 will be expected to include provisions for submission of limited access data sets as described below. Applicants are expected to include the costs of limited access data set preparation, with appropriate justification, in their budget requests. Funds awarded for limited access data set preparation will be restricted for use solely for that purpose and only upon release by the NHLBI.

In general the following types of studies will be included under this policy:

* Clinical trials and epidemiology studies that are supported by the U01 (cooperative agreement) mechanism AND have 500 or more participants

Appendix D: NHLBI Data Sharing Policy

* Trials or studies requesting \$500,000 direct costs or more in any one year and identified as being of high programmatic interest to the NHLBI, as indicated in the Institute's letter of agreement to accept assignment of the application

* Ancillary studies based on clinical trials or epidemiology studies that are required by this policy to provide limited access data sets.

Requests for exceptions to these guidelines will be considered by the NHLBI if adequately justified. Examples of adequate justification include: unavoidable and unanticipated delays in making data available within the parent study for analysis; presence of provisions in informed consent prohibiting LADS release; evidence of unacceptability of LADS release to communities under study; measurements on too small a subset of participants to be of scientific value. All such requests should be addressed to the Director of the Program Division funding the award.

Policies for data sharing from studies of American Indian or Alaska Native tribes and other sovereign entities will be developed with them and will be provided as available at a later date.

I. Introduction

The National Heart, Lung, and Blood Institute (NHLBI) has supported data collection from participants in numerous clinical trials and epidemiologic studies. These data from well-characterized population samples constitute an important scientific resource. It is the view of the NHLBI that their full value can only be realized if they are made available, under appropriate terms and conditions consistent with the informed consent provided by individual participants, in a timely manner to the largest possible number of qualified investigators.

Under no circumstances will data relating to an individual be distributed in any way that is inconsistent with his or her informed consent. Data sets without an informed consent permitting use by non-study researchers will only be released if the requester's IRB has approved a waiver of informed consent based on minimal risk to the participants [see Institutional Review Board section].

Data sets distributed under this policy include only "limited access data", i.e., records with personal identifiers and other variables that might enable individual participants to be identified, such as outliers, dates, and study sites, removed or otherwise modified. Because it may still be possible to combine the limited access data with other publicly available data and thereby determine with reasonable certainty the identity of individual participants, these data sets are not truly anonymous. They are, therefore, only provided to investigators who agree in advance to adhere to established policies for distribution.

Limited access data sets are available for NHLBI studies supported by contract and for selected studies supported by cooperative agreements or other grants. However, data will not be provided for limited access if the Institute deems them to be unreliable or invalid. All proposed data exclusions must be strongly justified and whether proposed by the study investigators or Institute staff, each one must be reviewed and approved by the director of the NHLBI program division that sponsored the study.

Appendix D: NHLBI Data Sharing Policy

II. Definitions

Data - Information collected and recorded from study participants through periodic examinations and follow-up contacts, not to include original specimens or images.

Commercial purpose - Data will be considered as being for a commercial purpose if they are to be used by an investigator who is an employee of a for-profit organization, if they are to be used by an investigator to satisfy a contractual relationship with a for-profit organization, or if they are to be used by an investigator as the basis for a consulting relationship with a for-profit organization. Data will also be considered as being for a commercial purpose if the investigator(s) take any affirmative steps to facilitate commercial use of results derived from the data.

Non-Commercial Purpose Data Set – A data set consisting of all records except those for participants who requested that their data not be shared beyond the initial study investigators.

Commercial Purpose Data Set – A data set consisting of all records except those for participants who requested that their data not be shared beyond the initial study investigators or used for commercial purposes.

Non-Commercial Purpose Pedigree/Genetic Data Set – A pedigree/genetic data set consisting of all pedigree and genetic data except those for participants who requested that their data not be shared beyond the initial study investigators.

Commercial Purpose Pedigree/Genetic Data Set – A pedigree/genetic data set consisting of all pedigree and genetic data except those for participants who requested that their data not be shared beyond the initial study investigators or used for commercial purposes.

III. Data Set Requests

A. Responsibilities of Investigators Seeking Access to Study Data

To ensure that the confidentiality and privacy of study participants are protected, all investigators seeking access to data from NHLBI-supported studies that are in the possession of the Institute must execute and submit with their requests the appropriate standard Distribution Agreement for each study. Because of the potential for identification of individual participants and consistent with the conditions included in the Distribution Agreements, investigators seeking access to study data must also submit an approval from their Institutional Review Board (IRB). An expedited review from the IRB is acceptable.

Unless a specific request for the Non-Commercial Purpose Data Set is received, investigators requesting access to study data will be provided with the Commercial Purpose Data Set. Investigators seeking access to the Non-Commercial Purpose Data Set must submit a signed statement affirming that they will not be using the data for a commercial purpose as defined above. Investigators who do so must recognize that if they subsequently develop results of potential commercial value, they will have to replicate those results using the Commercial Purpose Data Set before they can take any affirmative steps to facilitate commercial use of the results.

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Investigators interested in receiving a Pedigree/Genetic Data Set must specifically request it. Investigators seeking access to a Pedigree/Genetic Data Set must describe the specific need for access to it in the Research Project description of their signed Data Distribution Agreement. Investigators using these data sets are strongly discouraged from publishing individual pedigree structures and are prohibited from investigation into issues such as non-paternity.

Investigators should recognize that they are bound by the conditions of the relevant study Distribution Agreement. Failure to comply with it could result in denial of further access to NHLBI data sets. Moreover, violation of the confidentiality requirements in a Distribution Agreement may lead to legal action against the recipients of the data by study participants, their families, or the U.S. Government

B. Responsibilities of Study Investigators in Preparing Data Sets

Investigators in NHLBI studies covered by this policy are required as part of the terms and conditions of their awards to prepare and deliver to the NHLBI limited access data sets that satisfy NHLBI requirements. Included among them are documentation, elimination of personal identifiers, and modification of other data elements so as to reduce the likelihood that any individual participant can be identified.

Two limited access data sets, i.e., a Non-Commercial Purpose Data Set and a Commercial Purpose Data Set, and, if applicable, two pedigree/genetic data sets, i.e., a Non-Commercial Purpose Pedigree/Genetic Data Set and a Commercial Purpose Pedigree/Genetic Data Set, and associated documentation, must be provided in electronic form to the Institute. In addition, investigators must provide the Institute with two separate lists of participant identification numbers, one consisting of those participants who asked that their data not to be shared beyond the initial study investigators and the other of those participants who asked that their data not be used for commercial purposes.

Investigators in ancillary studies based on ongoing (parent) studies that are required by this policy to produce limited access data sets must submit ancillary study data to the NHLBI through the parent study Coordinating Center or limited access data submission process established by the parent study. Ancillary studies conducted on small subsets of a study sample may be appropriate for exclusion from limited access data sets; requests for their exclusion should be justified and addressed as described in the Introduction above.

1. *Documentation* – Documentation for limited access data sets must be comprehensive and sufficiently clear to enable investigators who are not familiar with a data set to use it. The documentation must include data collection forms, study procedures and protocols, descriptions of all variable recoding performed, and a list of major study publications.

In addition, a summary documentation file, usually called a "readme" file, is required. It must provide a complete overview of the data and a description of their use for investigators who are not familiar with the data set. It must also contain a brief description of the study (including a general orientation to the study, its components, and its examination and follow-up timeline), a listing of all limited access files being provided, a description of system requirements, a generation program code for installing a SAS file from the SAS export data file, and a frequency distribution for selected key variables.

2. *Data Storage and Format* – The data are to be stored on a CD ROM unless the investigators and the NHLBI mutually agree upon an alternative storage medium. Both the comprehensive documentation and the

Appendix D: NHLBI Data Sharing Policy

summary documentation must be prepared in a consistent format, either as a Word Perfect, MS Word, ASCII, or portable document format (PDF) file and included on the same storage medium as the limited access data set. To ensure access by users with disabilities, all PDF files must be created in Adobe Acrobat version 5.0 or higher. Documentation that is not available in electronic form, such as data collection forms, should be scanned into a graphics file, converted to a PDF file using Adobe Acrobat version 5.0 or higher, and saved on the same medium as the data set. Pedigree data should be provided in a format readable by standard genetic analysis programs such as SAGE and SOLAR, with one individual's data per line beginning with pedigree identifier, individual's id, father's id, mother's id, and individual's sex.

3. *Content of Limited Access Data* – In addition to summary information, limited access data sets also include for each participant those raw data elements (e.g., food item data or individual electrocardiographic lead scores) *that have not otherwise been processed into summary information.*
 - a. *Clinical Trials* – included are baseline, interim visit, ancillary data, and outcome data, along with laboratory measurements not otherwise summarized.
 - b. *Observational Epidemiology Studies* – included are all of the examination data obtained in each examination cycle, ancillary data, and/or all of the follow-up information available up to the last follow-up cycle cutoff date
4. *Timing of Release of Limited Access Data*
 - a. *Clinical Trials* – Data are prepared by the study coordinating center and sent to the NHLBI after publication of the primary clinical trial results. They are available for release once they are received and checked by the NHLBI. The data sets must be submitted to the NHLBI no later than 3 years after the final visit of the participants to their clinical trial sites or 2 years after the main paper of the trial has been published, whichever comes first.
 - b. *Observational Epidemiology Studies* – Epidemiology studies typically have an examination component and a mortality/morbidity follow-up component. Data from each cycle of an examination or follow-up component are prepared by the study coordinating center and sent to the NHLBI for distribution as a limited access data set no later than 3 years after the completion of each examination or follow-up cycle or 2 years after the baseline, follow-up, genetic, ancillary study, or other data set is finalized within the study for analysis for use in publication, whichever comes first.
 - c. *Ancillary Studies* – In those cases in which the timeline for an ancillary study differs from that of its parent study, the release date will relate to the timeline of the ancillary study.

IV. Procedures for Protection of Privacy for Limited Access Data Sets

A. Institute Review and Approval of Limited Access Preparation

The NHLBI requires that the data be provided in a manner that protects the privacy of study participants. The Institute requires appropriate documentation of the steps taken to protect their privacy in preparing a limited access data set. A summary of all proposed modifications and deletions to be made to a data set in

Appendix D: NHLBI Data Sharing Policy

preparing it for limited access must be submitted to and approved by the director of the division that sponsored the study prior to their implementation.

B. Guidelines for Limited Access Preparation

The following guidelines provide a framework for decision-making regarding preparation of limited access data sets:

1. All data for participants who refused to permit sharing their data with other researchers must be deleted from the Non-Commercial Purpose Data Set.
2. All data for participants who only refused to permit sharing their data for commercial purposes must also be deleted from the Commercial Purpose Data Set .
3. Participant identifiers:
 - a. Obvious identifiers (e.g., name, addresses, social security numbers, place of birth, city of birth, contact data) must be deleted.
 - b. New identification numbers must replace original identification numbers. Codes linking the new and original data should be sent to the NHLBI in a separate file, not included on the CD ROM, so that linkage may be made if necessary for future research.
- Variables that might lead to the identification of participants and of centers in multicenter studies, or variables that are sensitive, inaccurate, or of limited scientific utility:
 - a. Clinical center identifier -- In trials or studies that have only a few centers and relatively few participants per center, the data set should not contain center identifiers. In trials that have either many centers or a large number of participants per center, the data may offer little possibility of identifying individuals. For them, the investigators and the NHLBI will determine whether to include them on a case-by-case basis.
 - b. Interviewer or technician identification numbers must be recoded or deleted.
 - c. Sensitive data, including illicit drug use, risky behaviors (e.g., carrying a gun or exhibiting violent behavior), sexual behaviors, and selected medical conditions (e.g., alcoholism, HIV/AIDS) must be deleted.
 - d. Regional variables with little or no variation within a center because they could be used to identify that center must be deleted
 - e. Unedited, verbatim responses that are stored as text data (e.g., specified in "other" category) must be deleted
 - f. Pedigree and genetic data will be distributed in separate data sets only to investigators specifically requesting them. Genotyping data for any person in whom potential pedigree errors are detected must be deleted.

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- Dates: All dates should be coded relative to a specific reference point (e.g., date of randomization or study entry). This provides privacy protection for individuals known to be in a study who are known to have had some significant event (e.g., a myocardial infarction) on a particular date.
- Variables with low frequencies for some values, that might be used to identify participants, may be recoded. These might include:
 - a. Socioeconomic and demographic data (e.g., marital status, occupation, income, education, language, number of years married).
 - b. Household and family composition (e.g., number in household, number of siblings or children, ages of children or step-children, number of brothers and sisters, relationships, spouse in study).
 - c. Numbers of pregnancies, births, or multiple children within a birth.
 - d. Anthropometry measures (e.g., height, weight, waist girth, hip girth, body mass index).
 - e. Physical characteristics (e.g., missing limbs).
 - f. Detailed medication, hospitalization, and cause of death codes, especially those related to sensitive medical conditions as listed above, such as HIV/AIDS or psychiatric disorders.
 - g. Prior medical conditions with low frequency (e.g., group specific cancers into broader categories) and related questions such as age at diagnosis and current status
 - h. Parent and sibling medical history (e.g., parents' ages at death).
- Race/ethnicity and sex information when very few participants are in certain groups or cells.
 - a. Polychotomous variables: values or groups should be collapsed so as to ensure a minimum number of participants (e.g., at least 20) for each value within each race-sex cell.
 - b. Continuous variables: distributions should be truncated if needed to ensure that a minimum number of participants (e.g., at least 20) have the same highest and lowest values in each race-sex cell.
 - c. Dichotomous variables: data should either be grouped with other related variables so as to ensure a minimum number of participants (e.g., at least 20) in each race-sex cell or deleted
- The investigators may realize that other variables may make it easy to identify individuals. All such variables should be recoded or removed. The NHLBI program officer or project administrator should be consulted concerning such variables.

June 27, 2005

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