TITLE: Sleep-Disordered Breathing and CPAP after Adenotonsillectomy in Children

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2.2 SPECIFIC AIMS: Sleep-Disordered Breathing and CPAP after Adenotonsillectomy in Children

Obstructive sleep-disordered breathing (SDB) affects at least 2-3% of children and may have substantial adverse impact on behavior and cognition. Adenotonsillectomy (AT), the second most common surgical procedure in children, is now performed more often for suspected SDB than for any other indication. However, recent studies among an increasingly obese population now show something alarming: many if not most children still have SDB after AT, and many still suffer from residual neurobehavioral morbidity. Furthermore, the investigators' ongoing, 12-year, NIH-funded research has shown that standard preoperative polysomnographic measures of SDB do not consistently predict post-AT improvement in behavior and cognition. This may arise in part because many children after AT still have SDB, and because linear relationships between standard SDB measures and neurobehavioral morbidity may not exist. Even at subtle levels, SDB may promote significant neurobehavioral morbidity. Some have suggested that polysomnography may be more important after AT than before AT. However, in practice few children receive polysomnography before AT, and even fewer after AT, when continuous positive airway pressure (CPAP) could still provide definitive relief from SDB. Preliminary data from our group suggest that CPAP after AT is well-tolerated by most children and may provide significant benefit. However, virtually no published evidence exists to address critical clinical questions: which children benefit most from CPAP after AT; what role can clinical symptoms or polysomnography play in that determination; and what neurobehavioral gains are achieved by CPAP after AT?

The investigators therefore propose a highly practical, clinical study with **two main goals: (1) to assess the extent that behavior, cognition, and sleepiness in children can improve with CPAP after AT, and (2) to identify which patients stand to gain most from post-operative assessment and treatment.** This research will use reversible SDB-related neurobehavioral morbidity as the criteria by which to judge the utility of clinical symptoms and polysomnography in identification of candidates for CPAP after AT. Neurobehavioral outcomes will be assessed with instruments shown to be sensitive to SDB in the past. Clinical sleep symptoms will be assessed by use of a pediatric SDB questionnaire developed and validated by the investigators and now used around the world. Standard polysomnography will be supplemented by innovative approaches shown by the investigators to help identify subtle pediatric SDB. Subjects will be 5-12 years old and have had AT in recent months for suspected SDB. To enroll a reasonable distribution of children with and without obvious SDB symptoms after AT, the sample will be enriched selectively if necessary. *All analyses will be adjusted for body mass index z-scores.* These novel investigations will come at a critical juncture and could well transform clinical care for an exceedingly common and consequential childhood condition.

Aim 1: Complete parental sleep questionnaires, sleep laboratory-based nocturnal polysomnograms, Multiple Sleep Latency Tests of daytime sleepiness, parental behavioral ratings, and neuropsychological tests for *n=120* children 4 months after AT for clinically suspected or laboratory-confirmed SDB.
H1a: After AT, an SDB symptom scale will help identify children who have residual SDB on polysomnography.
H1b: After AT, residual problems with behavior, cognition, and sleepiness will show associations with persistent SDB as identified by the SDB scale or polysomnography.
Impact: Results will show that after AT, a symptom-based questionnaire can help identify children likely to have residual SDB, which in turn is a risk factor for persistent neurobehavioral morbidity. Clinicians and families will have, for the first time, data that can guide evaluation after an exceedingly common surgery.

Aim 2: *Randomize Aim 1 subjects to receive 6 months of standard clinical care (control group, n=40) vs. CPAP titration (CPAP group, n=80),* home use of CPAP, and monitored adherence; and then re-assess all subjects with all baseline sleep and neurobehavioral tests.
H2a: Among CPAP subjects who have adhered to the therapy, residual questionnaire or polysomnographic evidence of SDB from 4 months post-AT, as compared to no residual SDB, will predict greater improvement 10 months post-AT in hyperactive behavior, attention deficit, and sleepiness.
H2b: Among all CPAP subjects (n=80), neurobehavioral outcomes will improve more, from baseline to follow-up, among subjects who adhere successfully to CPAP than among those who do not.
H2c: Among all subjects (n=120), neurobehavioral outcomes will improve more among CPAP subjects than control subjects in an intent-to-treat analysis.

Impact: Results will demonstrate the clinical utility of an SDB questionnaire and polysomnography after AT; implicate post-AT residual SDB as a potential cause of persistent neurobehavioral problems; and suggest that successful treatment of post-AT SDB provides tangible clinical benefits.

2.3 RESEARCH STRATEGY

A. SIGNIFICANCE

A1. Pediatric sleep-disordered breathing (SDB) is common and consequential, especially for behavior and cognition. A growing volume of literature suggests that obstructive sleep apnea affects 2-3% of children.[1] The condition involves repeated upper airway narrowing or closure, which stops breathing, interrupts sleep, causes gas exchange abnormalities, and has profound effects on many different organs and systems. A milder form of SDB, in which a narrowed upper airway causes increased effort to breathe rather than discrete apneas or hypopneas,[2,3] was recently added to the definition of sleep apnea by the American Academy of Sleep Medicine,[4] and may affect many more of the estimated 10% of children who have habitual snoring. Sleep-disordered breathing represents a serious public health challenge as most affected children probably remain undiagnosed.[5] Consequences can have substantial impact on many aspects of health, among which neurobehavioral development may be the most sensitive.[6] Some of the earliest reports on children with SDB noted that many presented with inattention, hyperactivity, aggressive behavior, or a history of diagnosed and treated Attention Deficit / Hyperactivity Disorder (ADHD).[7,8] Subsequent sizable surveys, by the investigators as well as several other groups, generally showed consistent associations between symptoms of childhood SDB and the same constellation of neurobehavioral problems.[9-13] Brain, prefrontal cortex, and hippocampal mechanisms implicated as possible causes of neurobehavioral morbidity in SDB involve vulnerability to sleep fragmentation,[14,15] intermittent hypoxia,[16] oxidative stress,[17] inflammation,[18] neuronal injury,[19] and apoptosis.[20]

A2. Adenotonsillectomy (AT) improves, but may not eliminate SDB and its neurobehavioral morbidity. Once identified, pediatric SDB is most often treated by AT. This is one of the two most common surgeries performed in children.[21] A survey of North American otolaryngologists, performed by the investigators, showed that suspected SDB rivaled recurrent pharyngitis as the most common indication for ATs performed during a one-year period in approximately 24,000 children.[22] Moreover, early data suggested that AT was curative in approximately 80% of cases.[23] Other studies also suggested that substantial neurobehavioral improvements could be achieved in operated children.[2,7,24,25] However, recent data are more concerning. Sizeable series now show that 50% or more of children who undergo AT have some degree of residual SDB after the procedure.[26-28] The same studies strongly suggest that the reason may well be the obesity epidemic. Among 69 children, the odds ratio for persistent SDB in obese vs. non-obese subjects was about 4, even after adjustment for initial apnea severity.[29] Moreover, data from the investigators now confirm that not all neurobehavioral morbidity resolves after surgery. In a study of 78 children aged 5 – 12 years, 22 children had ADHD by DSM-IV criteria prior to surgery, and 11 qualified for this diagnosis one year after surgery.[30] Children whose ADHD did not resolve were those who still had evidence -- subtle but statistically significant and consequential -- of residual SDB after surgery.[31] Among all operated children, parent behavioral rating scales, cognitive performance, and psychiatric interviews no longer revealed statistically significant differences with controls, but might have done so in a larger sample as postoperative scores recovered less than half the pre-operative discrepancy between operated children and controls.[24,30] The fact that many children still have some morbidity after AT for SDB highlights the potential importance of identifying and treating any residual SDB.

A3. Debate exists on how to identify clinically significant SDB in children. Residual SDB detected after AT is usually not severe, as measured by polysomnography.[24,26] However, residual SDB even at low levels could have profound consequences for cognition and behavior, at least as suggested by studies of SDB severity and neurobehavioral problems prior to SDB treatment.[32] Several studies have now confirmed that neurobehavioral problems arise even at the lowest polysomnographic levels of SDB severity.[13,15,33] Comparisons of healthy controls to ADHD-diagnosed children not selected for any sleep problems show that the latter are more likely to have SDB, when definitions include the most subtle levels,[34,35] but not so consistently when children with the most mild SDB are excluded.[36,37] Several large studies have failed to confirm linear dose-response relationships between SDB, as measured on polysomnography, and neurobehavioral outcomes as rated by parents.[13,38-41] The investigators recently reported that children with SDB symptoms, but no sleep apnea on

polysomnography, in comparison to symptomatic children with positive sleep studies, have if anything more rather than less cognitive deficit and hyperactive behavior on objective testing and parental rating scales.[42]

These observations raise critical questions for clinical practice. Much debate in past years has centered on sleep specialists' contention that polysomnography should be routine prior to AT, vs. the opinion and practice of otolaryngologists, who rarely obtain a polysomnogram prior to AT for suspected SDB.[22] Instead, common practice among otolaryngologists, as supported by otolaryngology textbooks, is to base a decision to operate on information that can be gleaned from a history and physical. Some support for this approach was provided when a commonly used pediatric symptom-based SDB scale (developed and validated by the investigators,[43] see appendix) was tested against polysomnography as a predictor for neurobehavioral outcomes among children undergoing AT.[44] Questionnaire results, in comparison to several polysomnographic measures, predicted hyperactivity and daytime sleepiness, and their improvement after surgery, at least as well.

The 2002 recommendations from the American Academy of Pediatrics note that advice to obtain objective confirmation of SDB prior to surgery is predicated on the assumption that primary snoring, without clear sleep disruption or gas exchange abnormalities, is unlikely to cause symptoms.[6] Data since that time raise serious questions about this assumption. Children with SDB symptoms, with or without frank sleep apnea on standard polysomnographic measures, appear to benefit from AT.[24,45] However, AT (like uvulopalatopharyngoplasty in adults) may in some cases reduce or hide symptoms without eliminating SDB, and pediatric sleep specialists have now begun to wonder whether polysomnography may be even more important after AT than before the procedure. Testing in a sleep laboratory is routinely recommended after surgery for SDB in adults.[46] In contrast, polysomnography is rarely performed for children after AT, unless prominent symptoms persist, other risk factors remain, or the preoperative SDB was particularly severe.[47] The near total absence of data to indicate what levels of postoperative polysomnographic SDB findings merit further treatment has complicated not only clinical decisions, but research as well. For example, in a recent study of children after AT, residual SDB was defined – in the absence of data linking postoperative polysomnographic results to clinical outcomes – as an apnea / hypopnea index (AHI) > 3, even though the same study used the more generally recommended[4] AHI > 1 to help define treatable SDB before surgery.[27]

A4. Pediatric SDB can be treated effectively and safely by CPAP. For adults with SDB, continuous positive airway pressure (CPAP) is the mainstay of treatment and in the investigators' experience works well for approximately 80% of patients. Although some studies of adherence report success rates at this level, others that have used electronic monitoring have shown that as few as half of adult patients treated with CPAP use the machine for at least 4 hours on at least 5 nights per week.[48] Although far from ideal, a 50% adherence rate is no worse than that observed among adults with chronic conditions such as hypertension, and no worse than the average medication adherence found among children.[49]

Two 1995 reports of sizeable samples found that CPAP is highly effective in controlling childhood SDB, and is well tolerated in more than 80% of patients.[50,51] A smaller, randomized trial to compare CPAP with bilevel positive airway pressure (BPAP) found that one third of 29 participants aged 2 – 16 years dropped out by 6 months; CPAP and BPAP showed no difference in adherence or effectiveness; and mean nightly use recorded electronically was adequate on average (5.3 ± 2.5 hours per night) in subjects who finished the protocol.[52] Parental reports of adherence exceeded electronically recorded adherence, just as subjective CPAP use among adults exceeds electronically monitored use.[48] In a retrospective study of 46 children aged 7 – 19 years, all treated with PAP after AT, the intervention again controlled SDB well (in all subjects); 70% of subjects used PAP for more than 4 hours on 5 or more nights per week; parents overall estimated adherence well, though they overestimated machine use for those children documented to use it 4 hours or less per night; and adherence did not vary significantly by age, gender, BMI, or race.[53] In another retrospective study, 65 of 79 children aged 6 months to 18 years successfully used PAP, with a mean daily use of 4.7 hours.[54] The commitment and investment of the parents is particularly important. Initial trials of low pressure settings or behavioral intervention may be necessary in some cases.[55,56] Behavioral therapy can include positive reinforcement, differential positive reinforcement, counterconditioning, and graduated exposure.[55] These improved adherence in 75% of 20 non-compliant children in one study; parents usually considered the treatment successful and most reported improvements in children's mood, alertness, and learning.[55]

These trials of PAP in children also show that the therapy is safe. Mid-face hypoplasia, a reported but

probably uncommon complication of long-term PAP in young children,[57] did not occur in a trial of PAP for 6 months in 2 – 16 year-old children.[52] Other side effects are minor, and can include initial difficulty with masks, nasal congestion or drying, or skin irritation, one or more of which were reported in 11 of 46 subjects in one study.[53] In another study, side effects were minor, affected "a small percentage of children," were "easily addressed," and did not diminish adherence.[54]

Existing studies of PAP in children also have several limitations. All but one of the above were retrospective, and each included age ranges spanning a total of 12 to 19 years, during which SDB, its effects, and its treatment could vary significantly. Most studies either did not specify whether participants had had AT, or did specify that the majority of subjects were those with complicating medical disorders, such as Down syndrome or other clear reasons for developmental delay. Most of the studies discussed above included children with an AHI of 5 or more apneic events per hour of sleep, or did not specify the criteria used, which means that mild cases with an AHI between 1 and 5, in addition to those without clear SDB on standard polysomnographic measures, were most likely excluded. This is important because recent data now show that children with the mildest SDB findings on polysomnography, like adults, may still have prominent neurobehavioral morbidity.[24,58] None of the above studies included any objective measures of sleepiness or cognition, and none used validated parental rating scales to assess behavior. Finally, none explored post-AT residual symptoms, validated pediatric SDB questionnaires, or polysomnography as predictors of benefit from PAP.

Alternatives to CPAP, such as anti-inflammatory agents or orthodontic treatments, also show promise for post-AT residual SDB.[59] However, these approaches are not extensively studied and are likely to be effective for only the mildest cases of residual SDB. Compliance cannot be monitored as effectively as can adherence to CPAP with electronic usage meters. Perhaps most importantly for the research now proposed, in fully adherent subjects, essentially complete resolution of underlying residual SDB cannot be assumed for any treatment other than PAP. Therefore, PAP provides the best opportunity to study what clinical benefit children stand to gain through elimination of residual SDB, by any means, after AT.

A5. Whether CPAP for residual SDB after AT improves neurobehavioral outcomes remains virtually unexplored. Despite the availability of reports that document success with CPAP in children, with regard to adherence and amelioration of SDB, few have reported whether the CPAP improves SDB-related morbidity. In particular, virtually no data are available to examine whether CPAP further improves neurobehavioral outcomes after AT. Among 29 subjects aged 2 - 16 years in one prospective PAP trial, intervention was not associated with improved daytime behavior (according to parents), school performance, growth, or blood pressure, but was associated with improved parental assessments of sleepiness.[52] In a retrospective study of 46 children aged 7 – 19 years, parent-reported sleepiness and school problems did improve with PAP, and hyperactive behavior nearly showed significant improvement ($p=0.053$).[53] A recent abstract did document improvement in several different cognitive and behavioral spheres when CPAP was administered to 21 children aged 6 – 16 years with SDB, but did not specify how many of these children had already undergone AT.[60] Adherence to PAP correlated with improvements in parent-rated hyperactive behavior and subjective sleepiness. Neither of the above studies explored what pre-CPAP measures may predict neurobehavioral response to CPAP. In an era when obesity rates continue to rise unchecked; AT is increasingly performed for suspected SDB rather than pharyngitis; residual SDB may affect more than half of operated children; and unexplained hyperactivity is a hugely common and vexing problem for many families, data on the potential for neurobehavioral improvement when any SDB persists after AT would seem particularly critical.

A6. How candidates for CPAP after AT should be identified remains unexplored. While optimal strategies to identify childhood SDB that requires AT are still studied and debated, indications for additional treatment after AT have received virtually no attention. Among unoperated children, SDB is often defined in the setting of appropriate symptoms by an AHI that is at least somewhere between 1 and 5 events per hour of sleep. A population-based study of children in Arizona compared polysomnographic results to outcomes and suggested a cutoff of 2-3.[61] The current American Academy of Sleep Medicine definition,[4] at one event per hour of sleep, is likely to be a sensitive criterion for use in clinical practice. However, a threshold that is effective prior to AT may not provide an optimal cutoff after surgery. This is especially true given the inability of most studies to show a linear relationship between the AHI and the neurobehavioral morbidity likely to be most sensitive, compared to other forms of morbidity, to mild SDB. Although well conducted studies have now suggested that large numbers of children, after AT, have residual SDB, the use of preoperative SDB criteria postoperatively

may not have identified most effectively those individuals who stand to gain from further treatment.

A7. Summary of Significance. Findings from the proposed research will have critical impact on basic clinical practice questions that arise so frequently after an exceedingly common childhood procedure. Clinicians and families will have unique data from which they can begin to make judgments about the meaning of residual clinical symptoms after AT; the potential role for a validated SDB symptom questionnaire; the indications for post-operative polysomnography; how to select good candidates for CPAP after AT; and what neurobehavioral benefits to expect from CPAP. The most widely used pediatric SDB questionnaire and standard pediatric polysomnographic measures will provide the main explanatory variables for the study, but new and highly sensitive laboratory methods developed by the investigators also will be applied in a paradigm that could motivate refinement in current approaches to evaluation of children in sleep laboratories. Beyond clinical practice questions, results will also advance our understanding that post-AT, residual SDB may still be responsible for persistent neurobehavioral problems, and that definitive treatment of residual SDB could ameliorate behavior, cognitive impairment, and sleepiness that families and patients find highly undesirable. These data could identify key variables, determine effect sizes, and provide invaluable ground work to justify a multicenter randomized clinical trial to prove that neurobehavioral morbidity results from post-AT residual SDB, and to establish clear evidence-based recommendations for evaluation and treatment of SDB in this setting.

B. INNOVATION

The morbidity of postoperative, residual SDB, and outcomes of its treatment in children have scarcely been studied. The post-AT predictive value of clinical, questionnaire, and objective polysomnographic measures have not been assessed. The proposed research will therefore address several critical clinical questions for the first time. It will be performed by highly experienced investigators, in a setting proven to be most productive, using state-of-the-art polysomnography and widely accepted, standard measures that the PI helped to investigate and develop.[62,63] However, the proposed research also will capitalize on the investigators' leading efforts, during the past decade, to improve the clinical utility of pediatric polysomnography through innovative electronic analyses of polysomnographic data normally scored only by human eye. As described below, the investigators will apply 1) computer algorithms that link increased respiratory effort, outside apneas and hypopneas, to subtle EEG changes that may represent inspiratory microarousals; 2) automated quantification of esophageal pressure monitoring results; and 3) analysis of sleep dynamics that focus on durations of specific sleep stage bouts rather than more crude but traditional totals of minutes spent in each sleep stage. Each of these approaches holds promise, as explained below, for increasing the sensitivity and value of polysomnography in discrimination of clinically meaningful childhood SDB from normal and less consequential results. In short, therefore, the innovation of the proposed research rests on two sources: the protocol will begin to ask common, clinically relevant questions that have not been addressed before, and will complement standard assessment approaches with highly sensitive, new techniques that the investigators have invented, developed, validated, or investigated for several years.

C. APPROACH

C1. Overview. *We propose a single-center, randomized and controlled but not blinded clinical trial* to assess what variables predict further response to CPAP after AT (Figure 1). Potential inclusion of any child, regardless of post-operative polysomnographic results at 4 months, will allow the full spectrum of polysomnographic results to be tested as predictors of neurobehavioral response to CPAP. Standard cut-offs used to define clinically significant SDB remain untested in the post-AT setting, but will be applied first to test hypotheses 1a, 1b, and 2a. Other cut-offs and continuous measures that have been proposed by our group and others also will be tested in key exploratory analyses that could prove highly informative. The protocol will allow for example assessment of the possibility that clinical symptoms as detected on a questionnaire, but too insensitive to register on polysomnography, still deserve treatment.[44,45] *Every child who participates in this protocol will stand a chance to benefit. Two-thirds will receive CPAP; no standard care will be denied; and at the end of the study, summaries of sleep and neurobehavioral findings will be made available to all families, along with guidance on how to obtain follow-up clinical care for any remaining concerns.*

C2. Subjects. Recruitment will be directed by co-investigator Susan Garetz, MD, a University of Michigan pediatric otolaryngologist, with the assistance of 4 additional otolaryngologists in the Division of Pediatric

Otolaryngology, and 4 at St. Joseph Mercy Hospital in Ann Arbor. Both groups of surgeons have energetically supported recruitment for the PI's sleep research on children undergoing AT for the past 10 years. Surgeons or clinic office personnel will ask each parent or guardian of a child scheduled to undergo full AT for suspected SDB whether he or she would be willing to hear about the research. If so, a brief signed consent will be faxed to the investigators, who will initiate discussion by phone and then invite the family to the sleep laboratory to

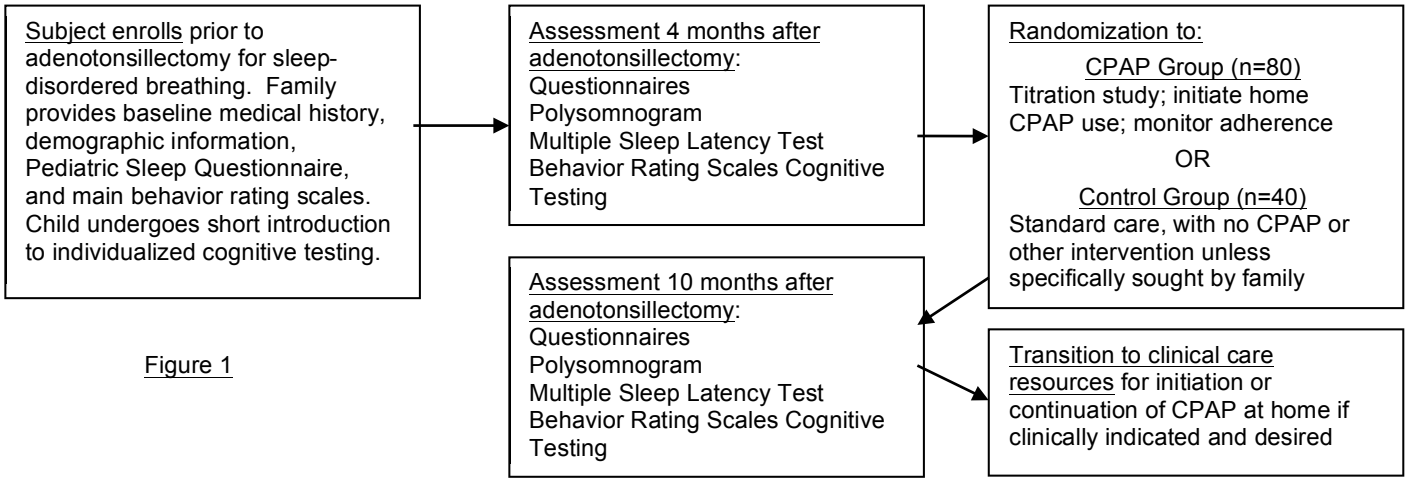

Figure 1

discuss the study in more detail. Occasionally parents may request referral to the study during phone contacts with the surgeon's office which will then fax the referral form to the study team. Children may also be referred into the program by sleep physicians, other providers, or their staff at UMHS and SJMHS sleep disorders centers and surgeons or their staff at Allegiance Health System. In some cases, interested parents may contact the study team directly for information about participation. To increase awareness of the study opportunity and encourage study participation, a copy of the IRB-approved study brochure and a reference to the study will be included with the UM Pediatric Otolaryngology follow-up letter which is sent to patients after adenotonsillectomy. Brochures are also available in all of the pediatric otolaryngology and sleep disorders clinics. Brochures may be mailed to families interested in research whose children are being referred into pediatric otolaryngology for possible adenotonsillectomy. At UMHS identification and recruitment of potentially eligible children will be assisted by MiChart Recruitment Alerts.

If the parent and eligible child are still interested, the parent will sign a full, written informed consent, the child will assent verbally, and any child over the age of 8 or able to comprehend the basic nature of the study will sign written assent. Families will also provide basic medical history and background information through a systematic interview and by granting access to medical records. Eligibility will be determined as soon as possible during the above process. Inclusion criteria, to be specified more completely in an operations manual, will include:

1) Age ≥5.00 and ≤12.99 years at study visit 2, consistent with the investigators' past work. Children younger than 5 years cannot be assessed with the same cognitive tests useful at older ages. Children older than 12, past puberty, may in their teenage years develop symptoms, signs, and neurobehavioral outcomes of SDB that resemble those of adults more than younger children.[64] Existing comparisons of age vs. more complicated Tanner staging, as peri-pubertal covariates of sleep outcomes, generally do not justify use of Tanner stages.[65]
2) Parental ability to speak and read English, for example on behavioral rating scales.
3) Absence of known or anticipated neurological, psychiatric, medical, or social factors likely to invalidate assessments, make adherence with CPAP highly unlikely, confound ability to demonstrate improvement with CPAP, or make local follow-up after AT or CPAP use unfeasible. Psychiatric conditions may be provoked or exacerbated by SDB, and those most commonly implicated – Attention Deficit/Hyperactivity Disorder, Conduct Disorder, and Oppositional Defiant Disorder – will not be exclusions. However, more pervasive conditions such as severe autism will be excluded.
4) Absence of chronic stimulant, hypnotic, or strongly sedating medication, unless families and their pediatricians are comfortable with 2-week drug holidays before the evaluations at 4 and 10 months after AT. Other chronic medications, in children without anticipated dose changes, will not be exclusions.

After careful consideration, neither specific SDB symptoms, laboratory evidence, nor neurobehavioral

comorbidity will be required initially to participate in this research. This will (1) allow participation by subjects with a wide range of SDB symptoms and neurobehavioral comorbidities; (2) facilitate detection of associations between these measures; and (3) avoid dependence on unsubstantiated assumptions as to what particular symptom, laboratory finding, or neurobehavioral deficit is necessary for improvement to occur on CPAP. The investigators realize that in practice, self-selection may enrich the sample with children whose families do have post-AT concerns about SDB symptoms. To avoid the possibility that such participants may be too infrequent, the investigators will assess the proportion of children with positive SDB questionnaire scores (> 0.33 [43]) after each group of 10 subjects has had AT. If this proportion falls below 50%, the investigators will enrich the sample, for example by requiring every other (i.e., every 2nd) participant to have a high SDB score, at both the initial pre-AT screen and re-assessment 4 months later, before randomization. For this purpose, the SDB score will be as useful, if not more useful, than polysomnography would be.[15,44] The proposed research is not epidemiologic, and validity will not suffer from selection bias or artificial enrichment of the sample.

Note that Addendum #1 provides for enrollment of subjects after adenotonsillectomy at or prior to study visit 2. This allows increased opportunity for interested families who are not able to schedule the pre-operative visit or who are referred to the study after their surgery to participate in this research. More information on this additional study arm Is provided in the addendum and the MOP.

C3. Procedures. Each participant will undergo a baseline, pre-randomization evaluation of sleep and neurobehavioral variables at 4 months after AT, as several months are required to ensure complete healing. Most of the neurobehavioral benefit achieved after AT for SDB accrues in the first 3 months (unpublished data from the investigators). After baseline assessments, all subjects will be randomized to CPAP or non-CPAP (standard care) groups. Group assignments will be made using a randomization algorithm, possibly with automatic adjustment that prospectively ensures balance between groups for SDB status, residual post-operative SDB symptoms, gender, age and/or BMI. Non-CPAP families will be contacted by the program manager for 6 months at intervals designed to replicate the frequency and nature of investigator contacts in the CPAP group. Discussion will focus on recuperation after AT, general health, and any suggestion of serious adverse effects that would warrant discontinuation of study participation and referral for clinical evaluation. These end-points would include recommendations by a child's pediatrician or otolaryngologist to pursue this option; development of a new, serious cardiopulmonary condition that makes prompt assessment and treatment for any residual SDB imperative; or emergence of serious academic or developmental concerns in the setting of obvious, persistent symptoms of SDB. Each questionable case will be brought by the program manager to the PI (section 6.5) for a decision and possible notification of the DSMB per the Data and Safety Management Plan guidelines.

Subjects randomized to the CPAP group will have prompt PAP titration in the sleep laboratory, and then use PAP (CPAP or BPAP) at home at the prescribed setting. Subjects will be fitted for masks in the sleep laboratory, with additional adjustments later, as necessary, by a respiratory therapist at MedEQUIP, the DME provider. Whenever possible, prior to their CPAP titration study or DME setup appointment, subjects will be issued a PAP mask for use at home while awake. This mask may not be identical to the mask that the child is fitted with at the setup appointment, but it will be sufficiently similar to allow the child to become familiar with the look and feel of a PAP mask. The parent or guardian will be instructed to have the child wear the mask for increasing intervals while awake to allow the child to acclimate to wearing a mask. The goal is to prepare the child for their upcoming CPAP titration study and PAP treatment. The child will be asked to practice wearing the mask several times daily until the setup appointment at which time the child will be fitted with a mask and issued their PAP machine and supplies.

Documentation of patient education on the use and potential safety concerns regarding PAP mask use without PAP for the acclimation process will be completed by the technologist issuing the mask or study staff. A copy of the patient education form and a summary of the acclimation protocol is provided in the Manual of Operations.

Adherence will be followed and fostered by Susan Armstrong, RN, who has extensive experience in CPAP desensitization for children in the Pediatric Sleep Clinic. Children and families with difficult adherence issues will be able to consult with Dawn Dore-Stites, PhD, a psychologist and faculty member of the multidisciplinary Pediatric Sleep and Behavior Clinic who is experienced with behavioral therapy to promote adherence. These

efforts to promote adherence will match or exceed those that have, in clinical practice here, produced a CPAP adherence rate of 67% (see section C9.7). Thresholds for referral are not well established in the literature, but possible examples might include:

a) Inability to tolerate CPAP during the CPAP titration trial;
b) Success during the CPAP titration trial but inability to use the mask/machine at home for more than 4 hours on the majority of nights over a 3 week period;
c) Failure to sustain use of CPAP after a period of success; or,
d) Failure to reinitiate CPAP therapy after a period off-treatment due to an upper respiratory illness or other interfering event.

The number and frequency of visits will depend on: (1) the child's current threshold; and (2) how the child and family advance through each step of the desensitization protocol. The decision to hold on a particular step of the desensitization program will be based on whether the homework was completed and/or whether the child's current level of anxiety or opposition is elevated. A recommendation to discontinue CPAP treatment may be made if the child or family has not progressed to another step in 2-4 weeks (depending on the number of visits during that time). Discontinuation of PAP treatment may occur after case consultation with other members of the study team to insure that all strategies have been considered. Additional effort to improve adherence is not desirable because this would not resemble practice available at most other clinical centers. In addition, varying levels of adherence will be necessary to test hypothesis 2b.

Approximately ten months after AT (six months after randomization), sleep studies (on steady PAP for the CPAP subjects, without PAP for controls) and neurobehavioral assessments will all be repeated. The sleep study is required to precede a valid Multiple Sleep Latency Test;[66] will allow confirmation in CPAP subjects that any SDB is well controlled; and will allow reassessment for residual SDB in the control group. The 6-month interval is selected to ensure adequate time for PAP habituation, neurobehavioral response to consistent use of PAP, and acceptably low risk of test-retest learning effects on cognitive measures. The outcome measures have been used by the investigators in two NIH-funded R01s (HD038461 and HL080941) over the past 10 years and all derive from well-validated, widely accepted instruments. The explanatory polysomnographic measures are all consistent with American Academy of Sleep Medicine 2007 standards.[63] Esophageal pressure monitoring, with which this laboratory has extensive clinical, research, and published experience,[24,67-70] will be used to provide a gold-standard assessment of respiratory effort. In addition, at least 3 highly innovative, most promising, and particularly sensitive computerized measures, all pioneered previously in children by the investigators, will be available to complement standard analyses. These include respiratory cycle-related EEG changes (RCREC) thought to reflect subtle but numerous and consequential inspiratory microarousals;[71-75] an analysis of sleep dynamics, which focus on continuity of sleep and specific sleep stage bouts rather than traditional totals of time spent in each stage;[76-79] and quantitative analysis of esophageal pressure swings during each respiratory cycle through the night.[75,80] Based on the investigators' preliminary data (see below and section C9.5), these automated measures may well improve the ability of pediatric polysomnography to distinguish children with and without clinically significant SDB and potential to benefit from CPAP.

One week prior to each sleep study, an investigator will call the family to confirm the appointment, verify absence of unexpected illness, and encourage completion of a one-week sleep log. Nocturnal sleep studies will be performed by registered, child-experienced sleep technologists in the 10-bed Michael S. Aldrich Sleep Disorders Laboratory, where 4 spacious rooms specifically designed to accommodate young children, and parents in a separate bed, are available also for research use. *Weight and height will be measured at the laboratory.* The next day, a Multiple Sleep Latency Test will be administered. Between naps, a trained technician will administer neuropsychological tests. All children will be tested after a night in the same environment, equivalent opportunities for good sleep, and measured total sleep times. During each child's testing, a parent will complete behavioral rating scales, the Pediatric Sleep Questionnaire (described above),[43,44] and a standard measure of socioeconomic status.[81] After the sleep studies at 4 months post-AT, submission of electronic adherence data (CPAP group) or other follow-up information (control group) at 7 months, and final assessments at 10 months, each child will receive a $30 gift certificate. After evaluations at 4 months and 10 months post-AT, each parent will receive $250 for their time spent on this research. Parents will also be compensated for timely, monthly follow-up contacts ($5 for each contact completed within 5

business days of the target follow-up call date), which are important in assessing possible safety concerns on study.

C4. Polysomnography. Sleep studies will include six EEG channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1 of the 10-20 international electrode placement system), 2 electro-oculogram channels (right and left outer canthi), chin and bilateral anterior tibialis surface EMG, 2 EKG leads, nasal and oral airflow (thermocouples), nasal pressure through pediatric sensor cannulae, esophageal pressure (using a pediatric esophageal balloon), thoracic and abdominal excursion (inductance plethysmography), and finger oximetry with pulse waveform. Esophageal pressure has been monitored by the investigators for clinical and research purposes for 15 years;[67] demonstrated to affect children's sleep negligibly;[67,68] successfully performed on the majority of the investigators' pediatric research subjects in the past;[68] and now listed among preferred measures for children[63] although many laboratories still have not adopted it. All recordings will be made on digital equipment (Compumedics, Inc.) with which the investigators have extensive laboratory-wide clinical and research experience since 2003. End-tidal or transcutaneous CO_2 will be monitored per the new (2012) AASM (American Academy of Sleep Medicine) guidelines for pediatric polysomnography. Both a research program manager and a physician will be on call by page during the studies.

Multiple Sleep Latency Tests will follow standard procedures.[66] As children have longer sleep latencies than adults, opportunities to fall asleep will be lengthened from the adult standard of 20 minutes to 30 minutes.[34,85] Five nap attempts will be scheduled 2 hours apart, usually at about 8:00, 10:00, 12:00, 2:00, and 4:00 pm. Parents will remain just outside the testing room. Urine drug screens will not be used because in 450 such tests for research here since 1999, none have turned up results that were both unexpected and meaningful.

An unmasked, board-certified sleep specialist will interpret each sleep study, not to provide study variables but rather to inform families and their physicians. Study results generally will not be communicated until after the participant has finished the entire protocol, when sleep and psychological test results are fully scored. However, an investigator will promptly communicate any finding that could have medically urgent significance for the patient, such as an unsuspected arrhythmia, paroxysmal EEG spikes, or severe residual SDB.

Nocturnal polysomnograms and Multiple Sleep Latency Tests will be scored by a single chief technologist (J. Fetterolf, RPSGT, REEGT) masked to subject identity. This technologist has meticulously scored about 1,000 pediatric sleep research studies in the past 10 years. Borderline polysomnographic features will be arbitrated between the technician and the PI. Scoring will be performed in batches: pre- and post-PAP studies of 5 subjects will be randomly ordered and presented for scoring. This procedure, used for two past R01s, assures that any subtle changes in scoring tendencies over time do not confound pre- vs. post-PAP comparisons. Scoring for sleep stages, respiratory events, periodic leg movements, and arousals will follow standard criteria for children.[63] Double-scoring of arousals and respiratory events, in 20% of the records, will be performed to generate a Kappa statistic for intra-rater reliability. Inter-rater reliability will also be determined by having another experienced polysomnographic technologist score these same records.

For Multiple Sleep Latency Tests, the sleep latency of each nap will be scored as the time between lights out and the first epoch of stage 1 sleep.[66] The mean sleep latency across naps is the most well-validated and commonly used objective measure of daytime sleepiness in both adults and children.[86,87] Childhood sleepiness as a continuous variable for research purposes can be detected in SDB patients as young as 3 years old by questionnaires[43] and by Multiple Sleep Latency Tests.[85]

Respiratory cycle-related EEG changes (RCREC) will be computed as previously described.[71,74] Briefly, a central EEG lead and airflow from a thermocouple signal are analyzed. Signals from computer-detected regions of apnea or hypopnea (generally a small minority of the total recording time) are excluded. Remaining respiratory cycle airflow signals are smoothed and divided into quarters (early expiration, late expiration, early inspiration, and late inspiration); EEG spectral power within pre-determined frequency ranges of interest are computed by digital filtering; and the mean power for each quarter-cycle, relative to power over the entire respiratory cycle, is computed. Results for each quarter-cycle segment are averaged over thousands of respiratory cycles (generally several hours of recording) and the maximal difference between mean relative segment powers is defined, for any given subject and within the targeted EEG frequency band, as the RCREC value. The investigators have shown that RCREC are greater in children with SDB than those without SDB;[72]

RCREC improve after adenotonsillectomy;[72] they correlate with subjective and objective measures of sleepiness in children and adults;[72-74] this association persists after accounting for objective measures of SDB severity;[73,74] RCREC correlates with esophageal pressure swings but is far from completely explained by them;[75] and RCREC may well reflect subtle but numerous cortical microarousals in response to labored non-apneic breathing that pervades much of the night for patients with SDB.[73] In the research now proposed, sigma range (12-15 Hz) RCREC will be the main focus, as RCREC within this range have proved most sensitive to sleepiness in both adults and children.[73,74]

Esophageal pressure swings for all respiratory cycles, after exclusion of irregular breaths and artifacts, will be computed automatically using an algorithm developed by the investigators and previously shown to match well with much more time-consuming visual analyses.[75,80] Sleep dynamics analyses will involve computation of the mean lengths of contiguous sleep and specific sleep stage bouts. The investigators have previously shown that these data may characterize sleep fragmentation more sensitively, in children with SDB,[76] adults with fibromyalgia,[77] or adults with asthma,[88] than do arousals or standard analyses of sleep stages as total minutes, percentages of total sleep time, or sleep efficiency.

C5. Neurobehavioral Assessments. Standardized, well-validated tests will be used to assess outcomes widely recognized as some of the most important and sensitive in childhood SDB. As noted above, many studies of SDB morbidity have found associations with inattentive, hyperactive, and aggressive behavior, and with cognitive problems such as attention deficit.[15] Behavioral and cognitive measures, confirmed to be useful in our previous studies of childhood SDB[42] and in related work by our group and others,[15] will provide outcomes for this study. Validated parental rating scales for inattention, hyperactivity, general behavioral issues, and quality of life will best assess the primary complaints parents often communicate and clinicians seek to address. Other outcomes will include neuropsychological measures of short-term attention, visuospatial problem solving, executive functioning, and memory. These measures are important for assessment of cognitive changes in treated and untreated patients with sleep disorders,[15] as well as attention deficit and other medical disorders,[89,90] and many are available in multiple, equated forms to reduce practice effects.[91-95] General intelligence and academic achievement will be briefly assessed, because in some reports they are sensitive to SDB[34] and because they should be taken into account when other specific outcomes are analyzed. Although the investigators have in previous research on AT included psychiatric evaluations, these are now omitted because AT effectively reduces the rates of DSM-IV diagnoses to a level that would be difficult to study without an enormous postoperative sample. In contrast, continuous measures provided postoperatively by parental behavior rating scales, cognitive assessments, and Multiple Sleep Latency Tests do not reach levels identical to those of controls and should be more sensitive to benefits from CPAP after AT.

Behavioral Assessments: Standardized rating scales to be completed by a child's parent or guardian will include the Conners' Parent Rating Scales (CPRS-R:L)[96] and the Child Behavior Checklist (CBCL),[97] with the primary study outcome measure, Behavioral Index, being constructed from the sum of the T-scores from the Conners' ADHD Index and CBCL Attention Deficit/Hyperactivity Problems. Parents also will complete the CPRS-R:L and CBCL at the pre-operative meeting after signing the consent materials with their child. Although not representing a primary outcome point for this study, this assessment will serve to familiarize parents with the process of observational reporting on their child; provide important information or grouping variables for secondary analyses; and help to confirm that CPAP and control groups have equivalent behavior at baseline. Because of the importance consistently reported for the measurement of executive functioning in children with SDB,[15] the Behavior Rating Inventory of Executive Functioning (BRIEF)[98] also will be completed. Finally, quality of life will be measured from both the Peds-QL parent and child forms.[99] The CPRS-R:L, CBCL, and BRIEF are available in teacher forms that will allow secondary, corroborative assessment in both a home and school environment, and help address any evident[42] parental bias. Through experience in our laboratory and work with the multicenter Childhood Adenotonsillectomy (CHAT) trial, for which our center directs quality assurance and monitoring of behavioral and cognitive assessments, we have developed techniques to sustain strong return rates for teacher ratings.

Any or all survey instruments used in this study may be administered as paper forms or electronic versions, which may be delivered by email or via a web-based software system such as Qualtrics, or as a combination of paper and pencil and electronic formats, depending on the form type and the reporter (child, parent or teacher). *Any instrument for survey over the internet will be or is being developed through the auspices of the computer*

support group in Psychiatry and MCIT to be sure it is HIPPA compliant, as are current measures employed in Psychiatry for their patient metrics.

Cognitive Assessments. Tests will be administered by an experienced, neuropsychologist-supervised psychometrist who is well trained to maintain children's motivation and monitor the need for rest breaks or changes in conditions. Each child also will receive a brief introduction to face-to-face testing using CogState (described below) during the time just following consent signing. As many children will not have had the experience of being tested before, this introduction will reduce apprehension and familiarize each child with the types of materials to be tested. The total testing time for post-AT sessions will be approximately 2 hours, spread between nap studies. This is less time than routine clinical evaluations (usually 4-8 hours). All specific test sessions will occur at the same time of day, without variance between subjects or test and retest visits.

The Attention/Executive Functions domain score of the NEPSY-II[100] and the computerized continuous performance test, Integrated Variables of Attention,[101] will comprehensively cover short term and sustained attention, vigilance, impulsivity, and executive ability. Overall intelligence and academic achievement will be assessed briefly using the two Stanford-Binet, 5th Edition (SB5) "routing tests", Matrices and Vocabulary[102] and selected Woodcock Johnson-III[91] subtests (Letter Word Identification, Reading Fluency, Calculation, and Applied Problems). The Selective Reminding Test is sensitive to children's memory,[95] specifically verbal encoding and retrieval. Speed and control of fine motor ability will be measured with the Purdue Pegboard.[103] Finally, the brief computerized CogState battery will provide valid indices of processing speed, working memory, executive functioning, and memory in a combined measure that remains stable over time, incorporates simple response requirements and self-contained training modules, and has proven inherently interesting and motivating, and sensitive to subtle cognitive change in children.[94] This test also includes the Groton Maze Test,[92] a brief, computerized measure of psychomotor speed and visuospatial problem solving.

As newer versions of these or other equivalent neurobehavioral tests are released, they may be substituted for currently available versions, as deemed necessary by the PI and CoInvestigators on the project to meet the project aims. For example, an equivalent battery of neurobehavioral and quality of life measures has been developed as part of a NIH Toolbox for the Assessment of Neurological and Behavioral Function and is expected to become available in the near future. Because the NIH toolbox battery spans ages 3-85 and is designed to minimize subject burden, components of this battery may be substituted, whenever appropriate, on this study.

C6. Intervention. All CPAP group participants will have a CPAP titration study shortly after the initial post-AT polysomnogram. During this additional night in the sleep laboratory, pediatric core technologists will fit each child with an appropriate mask, monitor sleep and breathing as above, and remotely increase administered pressures until SDB resolves. Each record will be scored as above, but by any available registered pediatric sleep technologist (not waiting for batching) so that an investigator (Dr. Hoban) can promptly review the study and determine an ideal pressure setting to prescribe. An experienced respiratory therapist at MedEQUIP will then meet with the family, issue them a CPAP machine and mask at no cost to the family, educate them about CPAP use, and serve as a contact should any mechanical problems arise.

Approximately every 30 days (or more often as necessary) over the next 6 months, the DME provider or study team staff will review compliance data that is remotely downloaded via modems on the PAP machines. Alternatively, data downloads may also be done onsite from the SD memory cards in the PAP machines. Adherence and therapeutic data will be stored in a secure office of Encore Anywhere, a HIPAA compliant, web-based patient compliance management system provided by Philips Respironics, the manufacturer of the PAP machines used on this protocol. Restricted access to Encore Anywhere "offices" is provided by Philips Respironics, and the offices are password protected. The study data files will be maintained in a separate office from the UMHS clinical patient compliance database in Encore Anywhere. This will restrict casual access to the research data by other UM providers or staff. Linkable identifiers will be used in the place of subject names to help maintain privacy for research participants.

Detailed plans to promote adherence, to be elaborated in the operations manual, will include phone calls approximately weekly for the first 3 weeks to detect any problems early; a meeting with the study nurse or

other investigators at 3 months; additional meetings or phone interviews every 4-6 weeks; further intervention of Susan Armstrong, RN (research assistant and experienced pediatric sleep clinic nurse) as needed; and referral to Dawn Dore-Stites, PhD (co-investigator and psychologist in Pediatric Sleep and Behavior Clinic) when adherence is problematic. *All no-CPAP group participants will receive a series of contacts from an investigator, to control for this potential confound (see Introduction), including an interval visit with the study nurse or other investigators between study visits 2 and 4, whenever possible; assistance with referral at the end of the study for any desired or indicated clinical follow-up; and research-funded PAP equipment if a child without insurance coverage requires treatment. A brief 7-items survey will be administered to children and parents (both arms of the study) at the interval (~3month followup) clinic visit with study staff and again at the endpoint visit to elicit additional information on their experience or health status during their participation. Copies of the survey are available in the Manual of Procedures.*

C7. Outcome Measures:

This section defines the outcome measures to be gathered for this trial, classified into primary, secondary and exploratory. Other measures referred to anywhere within the protocol are to be considered baseline, exploratory for cross-analyses or safety related, as appropriate. Study visit 2 (SV2) represents the initial polysomnogram approximately 4 months following AT and study visit 4 (SV4) represents the final polysomnogram approximately 6 months later (equivalent to approximately 10 months after AT).

(a) Primary Outcome Measure:

1. Neurobehavioral change (hypothesis 2c CPAP vs controls intent to treat)
Change in **behavioral index** following 6 months of CPAP vs. no CPAP use by children after AT

(b) Secondary Outcome Measures:

1. Neurocognitive change after AT (hypothesis 2c CPAP vs controls intent to treat)
Change in **NIH Toolbox Total Composite Score Age Adjusted** following 6 months of CPAP vs. no CPAP use by children after AT
2. Change in subjective sleepiness after AT (hypothesis 2c CPAP vs controls intent to treat)
Change in **Epworth Sleepiness Scale score** following 6 months of CPAP vs. no CPAP use by children after AT
3. Change in objective sleepiness after AT (hypothesis 2c CPAP vs controls intent to treat)
Change in **MSLT** following 6 months of CPAP vs. no CPAP use by children after AT
4. Change in quality of life (hypothesis 2c CPAP vs controls intent to treat)
Change in **PedsQL** following 6 months of CPAP vs. no CPAP use by children after AT
5. For CPAP subjects, neurobehavioral outcomes will improve more from baseline to follow up among those who have adhered to CPAP than those who are non-adherent (hypothesis 2b)
Change in **behavioral index** from SV2 to SV4 in adherent vs non-adherent CPAP users
6. For CPAP subjects, neurobehavioral outcomes will improve more from baseline to follow up among those who have adhered to CPAP than those who are non-adherent (hypothesis 2b)
Change in **NIH Toolbox Total Composite Score Age Adjusted** from SV2 to SV4 in adherent vs non-adhere
7. For CPAP subjects, neurobehavioral outcomes will improve more from baseline to follow up among those who have adhered to CPAP than those who are non-adherent (hypothesis 2b)
Change in **ESS** from SV2 to SV4 in adherent vs non-adherent CPAP users
8. For CPAP subjects, neurobehavioral outcomes will improve more from baseline to follow up among those who have adhered to CPAP than those who are non-adherent (hypothesis 2b)
Change in **MSLT** from SV2 to SV4 in adherent vs non-adherent CPAP users
9. For CPAP subjects, neurobehavioral outcomes will improve more from baseline to follow up among those who have adhered to CPAP than those who are non-adherent (hypothesis 2b)
Change in **PedsQL** from SV2 to SV4 in adherent vs non-adherent CPAP users
10. Among adherent CPAP users residual SRBD score at SV2 will predict greater improvement at SV4 for behavior (hypothesis 2a)
Change in **behavioral index** from SV2 to SV4 in CPAP adherent subjects will be associated with SRBD score at SV2
11. Among adherent CPAP users residual SRBD score at SV2 will predict greater improvement at SV4 for cognition (hypothesis 2a)
Change in **NIH Toolbox Total Composite Score Age Adjusted** from SV2 to SV4 in CPAP adherent subjects

will be associated with SRBD score at SV2
12. Among adherent CPAP users residual SRDB score at SV2 will predict greater improvement at SV4 for subjective sleepiness (hypothesis 2a)
Change in **ESS** from SV2 to SV4 in CPAP adherent subjects will be associated with SRBD score at SV2
13. Among adherent CPAP users residual SRDB score at SV2 will predict greater improvement at SV4 for objective sleepiness (hypothesis 2a)
Change in **MSLT** from SV2 to SV4 in CPAP adherent subjects will be associated with SRBD score at SV2
14. Among adherent CPAP users residual SRDB score at SV2 will predict greater improvement at SV4 for quality of life (hypothesis 2a
Change in **PedsQL** from SV2 to SV4 in CPAP adherent subjects will be associated with SRBD score at SV2
15. Among adherent CPAP users AHI at SV2 will predict greater improvement at SV4 for behavior (hypothesis 2a)
Change in **behavioral index** from SV2 to SV4 in CPAP adherent subjects will be associated with AHI at SV2
16. Among adherent CPAP users AHI at SV2 will predict greater improvement at SV4 for cognition (hypothesis 2a)
Change in **NIH Toolbox Total Composite Score Age Adjusted** from SV2 to SV4 in CPAP adherent subjects will be associated with AHI at SV2
17. Among adherent CPAP users AHI at SV2 will predict greater improvement at SV4 for subjective sleepiness (hypothesis 2a)
Change in **ESS** from SV2 to SV4 in CPAP adherent subjects will be associated with AHI at SV2
18. Among adherent CPAP users AHI at SV2 will predict greater improvement at SV4 for sleepiness (hypothesis 2a)
Change in **MSLT** from SV2 to SV4 in CPAP adherent subjects will be associated with AHI at SV2
19. Among adherent CPAP users AHI at SV2 will predict greater improvement at SV4 for quality of life (hypothesis 2a)
Change in **PedsQL** from SV2 to SV4 in CPAP adherent subjects will be associated with AHI at SV2

(c) Exploratory Outcome Measures;
Measures of academic achievement, fluid cognition, and REREC are all considered exploratory.

C8. Analyses. For Hypothesis 1a, post-AT SDB as an outcome variable will be defined as a respiratory disturbance index (RDI) ≥ 1 obstructive or mixed apnea, hypopnea, or respiratory effort-related arousal per hour of sleep.[63] The 22-item SDB scale score (on a continuous scale from 0.0 to 1.0 [43]) will provide the main explanatory variable. Logistic regression models will be assessed for sensitivity to potential covariates or confounds, including age, gender, race, body mass index z-score, and socioeconomic status. Secondary analyses will focus on RDI as a continuous outcome; validated snoring, sleepiness, and behavior subscales within the SDB scale; habitual snoring as a single, previously informative[9,104] question-item; and most importantly SDB data generated by innovative algorithms, as described above, exploratory analyses for RCREC, esophageal pressures, and sleep dynamics. For Hypothesis 1b, multiple linear regression models will be constructed to assess cross-sectional associations between each neurobehavioral morbidity (the Behavioral Index being the primary outcome) and the SDB questionnaire score or RDI as the main explanatory variable. Models of the SDB questionnaire will use a slightly shortened, 16-item version (as previously [9,105]) to exclude behavioral questions that would correlate with outcome measures for artificial reasons. Covariates as above will be taken into account. Secondary analyses will 1) assess the impact of SDB scores or RDI on other behavioral and cognitive measures; 2) take IQ and achievement into account within the main models; and 3) test the 3 newer, computed SDB measures in place of RDI. To assess Hypothesis 2a, the investigators will define adequate adherence as at least 4 hours of electronically recorded CPAP use per night, on average over the most recent 3 months on treatment. A series of multiple linear regression models will be used, with post-PAP improvement in neurobehavioral variables as outcomes. The pre-CPAP SDB questionnaire scores or RDI will serve as the main explanatory variables. Secondary analyses will use the 3 SDB measures generated by computer algorithms as the explanatory variables. To assess Hypothesis 2b, the same outcomes will be regressed on CPAP adherent vs. non-adherent categorization, as well as (secondarily) a continuous measure of adherence as defined by mean hours of nightly use during the last 3 months of the trial. As with Hypotheses 1a and 1b, models for 2a and 2b also will be assessed after adjustment for similar potential covariates or confounds. To assess Hypothesis 2c, intent-to-treat analyses will use models that regress each primary neurobehavioral outcome on initial CPAP vs. control group assignment, after adjustment for BMI z-scores, age,

gender, race, and socioeconomic status. Exploratory models will in addition consider RDI (or computer algorithm proxy measures) and PSQ scores at 4 or 10 months post-AT, to assess whether residual SDB on these measures may explain differences in neurobehavioral outcomes. Exploratory analyses will also compare outcomes between CPAP-adherent subjects and controls, to assess (by contrast to the primary intent-to-treat analysis) what benefit may be lost by poor adherence, cross-overs, or drop outs.

In addition to standard SAS and Excel databases, REDCap (Research Electronic Data Capture) may be used for database development and data capture and management on this study as well as in tracking study activity. REDCap is a web-based electronic data capture system available under contract to the University of Michigan. Developed by Vanderbilt University, with collaboration from a consortium of institutional partners, REDCap provides a secure, web-based application designed to support data capture for research studies. REDCap is endorsed by the Michigan Institute for Clinical and Health Research (MICHR) and is part of larger data collection initiatives under the CTSA grant. REDCap was developed specifically around HIPAA-Security guidelines and has been disseminated for use locally at other institutions. By mid-2011, REDCap was being used by more than 200 academic/nonprofit consortium partners on six continents supporting more than 20,000 research end-users (www.project-redcap.org).

At the University of Michigan, the application is restricted to users on the UMHS Internal Network requiring a secure connection to communicate with U-M services i.e. VPN. The database is stored on a server separate from the application. Servers are maintained and supported by the Medical School Information Services (MSIS). REDCap Application support and services are provided by the Michigan Institute for Clinical and Health Research (MICHR).

C9. Sample Size. Plans are based on extensive preliminary data from the investigators on effects of AT for childhood SDB, and on the only quantitative preliminary data published, in 2009, for the neurobehavioral effects of CPAP in children with obstructive sleep apnea.[60] Data from our group (section C9.3) show that the proportion of children, among those who undergo AT here for SDB, who have residual SDB 6 months later is about 50% or more, depending on criteria used to define SDB. Children with mildest SDB can have robust improvement in behavior, as measured with particular relevance for the current application on the Conners' ADHD Index. This improvement, by 0.5 standard deviations, is at least as strong as the that observed in more severe apneics.[24,30,42] Yet, more than 0.5 standard deviations still separate Connors' scores in post-AT SDB patients from those in controls.[24] The CPAP intervention we propose is a gold-standard widely believed to completely remedy any residual airway obstruction in adherent subjects. The CPAP may well, therefore, prove to be a more definitive treatment than AT in final elimination of even mild SDB. In a study of 21 children aged 6 to 16 years, with SDB of any severity and unselected for neurobehavioral problems, 3 months of CPAP was associated with robust improvement in inattention and hyperactivity on the Conners' scale ($p<.001$ despite the limited sample) and in subjective sleepiness (Epworth, $p<.001$).[60] Adherence with PAP correlated with improvement in the Conners' measure ($r=.48$, $p=.03$) and the Epworth ($r=.58$, $p=.006$). These results emerged despite use of PAP by the subjects on only 56% of all nights on average. Our preliminary data (C9.7) suggest that we can expect about 67% our subjects to show adequate adherence.

Given these observations, we anticipate conservatively that a sample of 80 CPAP subjects who complete the protocol will contain about 40 with SDB (RDI>1); that 53 will be adherent with PAP; and that most subjects with RDI>1 along with some subjects who have RDI<1 (but perhaps SDB symptoms) will benefit from PAP. For hypothesis 1a, to test for a correlation between SDB questionnaire scores and polysomnographically-defined SDB, we will have 80% power to detect a clinically meaningful Spearman correlation *rho* ≥ 0.25 with $\alpha=.05$. Similarly, for hypothesis 1b, which focuses on an association between residual neurobehavioral problems and either SDB questionnaire scores or RDI, we will be able to detect a *rho* ≥ 0.25. For hypothesis 2a, with about 27 post-AT, CPAP-adherent subjects who have RDI>1 and 26 who have RDI<1, we will have 82% power to reject the null hypothesis (that the mean 6-month change scores in the Behavioral Index for the two groups are equal) if the effect size is ≥ 0.8. The likelihood of this result is based on observations in our previous studies with the Conners' ADHD Index, which is a main component of the Behavioral Index now proposed. Based on improvement we have measured in the past after AT for children with mildest levels of SDB, for the current hypothesis 2b, in which we will compare about 53 treated (adherent) to 27 non-treated (non-adherent) residual apneics, we should have power of 0.78 to detect an effect size ≥ 0.65. This effect size is substantially smaller than that implied by the correlations above among 21 children[60] and by our own preliminary data below. *For*

hypothesis 2c, comparison of 80 CPAP-treated subjects to 40 controls should provide 80% power to detect a Behavioral Index difference between groups (effect size) ≥ 0.55. The 120 subjects will be recruited from the 2,475 children aged 5-12 years anticipated to have AT at the two otolaryngology practices during 3 years and 4 months of study enrollment. *In each of two previous R01 studies here that followed children for 12 or 6 months after AT, attrition was only 5% with careful attention to each family from an experienced project manager. The study now proposed will conservatively anticipate 10% attrition, and target enrollment of 132 subjects.*

C10. Preliminary Studies.

C10.1 The investigators are experienced and well prepared to conduct the proposed research. The investigators have held continuous funding from the NIH since 1997 to study childhood SDB, its assessment by subjective and objective means, and its neurobehavioral outcomes. Findings of this highly multidisciplinary group helped to call attention to the association between SDB and inattention, hyperactive behavior, and aggression in children.[9,104,105] In one of the first long-term prospective studies of snoring, they showed that it predicts incident hyperactivity 4 years later.[106] They demonstrated that although daytime sleepiness may not be obvious in children with SDB, it can often be detected by history or questionnaire, or by objective testing.[74] They have studied treatment of SDB, by AT, for 11 years. They have examined in detail the psychiatric and neuropsychological outcomes of treatment for pediatric SDB.[30,42] They have advanced the ability to monitor outcome-relevant, objective features of subtle pediatric SDB.[72,74,75] In particular, they are experienced with esophageal pressure monitoring to assess respiratory effort optimally, and have shown that the procedure does not substantially disrupt children's sleep.[67,68] They have developed new approaches to assess subtle effects of childhood SDB on the brain. For example, they were the first to characterize respiratory cycle-related EEG changes (RCREC),[71,72] as well as sleep stage dynamics in children.[76]

C10.2. The pediatric SDB questionnaire to be used in this study was developed and validated by the investigators, and shown to be useful in many research studies. The 22-item SDB component of the Pediatric Sleep Questionnaire asks about chronic snoring, snorting, observed apneas, other breathing difficulties, ancillary symptoms, and behavioral signs (see appendix), each of which individually predicts childhood SDB as confirmed by polysomnography.[43] The scale can be licensed online from the University of Michigan by any investigator at no cost. When tested against polysomnographically-defined pediatric SDB, the SDB scale showed a sensitivity of 0.81, specificity of 0.87, and overall classification accuracy of 85%, with good internal consistency and test-retest reliability.[43] In a subsequent study of 78 children who underwent AT for clinical purposes, and 27 controls, the SDB scale identified subjects with polysomnographically-confirmed SDB both before and one year after AT.[44] The SDB scale predicted current hyperactive behavior, sleepiness (mean sleep latency), and their responses to AT at least as well as sleep studies did. However, these important findings require confirmation, as the original aims of the research did not include these analyses. Furthermore, no data were collected on response to PAP. Nonetheless, the SDB scale is now used in many studies at the University of Michigan, elsewhere in the U.S.,[107-109] and around the world,[110-112] where it has been translated (at minimum) into Spanish, German, Chinese, and Turkish, with Korean and Portuguese versions in progress.

C10.3. Pediatric SDB often fails to resolve completely after AT. Obstructive sleep apnea in children is defined in part by an RDI > 1.[4,63] In the investigators' recently completed, longitudinal cohort of 135 children who had AT for clinical indications, 89 (66%) had an RDI > 1 six months after AT. Using a slightly more conservative cut-off to define abnormality,[113] based on statistical analyses of sizeable samples, 63 (47%) of the 135 subjects still had an RDI ≥ 1.5 after AT. However, the number of children after AT who might benefit from additional treatment for SDB remains unknown, and could be higher, lower, or more complicated than the numbers identified by the above RDI thresholds. Studies have not assessed what polysomnographic criteria are most informative, as judged by response to further treatment.[113] Potential for meaningful treatment response, rather than a somewhat arbitrary polysomnographic number, can best determine what clinical care should be offered.

C10.4. Many children have residual neurobehavioral morbidity after AT. Previous data from the investigators have demonstrated clear improvement in objective measures of attention, parental ratings of hyperactive behavior, and both subjective and objective measures of daytime sleepiness one year after AT.[24,30] The magnitude of these improvements has approached one half of a standard deviation and is clearly meaningful clinically. However, many children are not cured, and a minority actually worsen. The investigators have hypothesized that brain injury earlier in childhood may only manifest later in a developmental trajectory.[106] Another distinct possibility, however, is that low levels of residual SDB after surgery continue to provoke

neurobehavioral morbidity. Patients with symptoms of SDB but minimal or no evidence of frank sleep apnea on standard polysomnography, in comparison to those with clearly positive studies, have sometimes been found by the investigators and others to have equivalent[70] or even worse[42,58,114] neurobehavioral morbidity.

C10.5. Subtle SDB measures on polysomnography may identify children who stand to benefit from PAP after AT. Standard polysomnographic measures have not always correlated well with neurobehavioral morbidity widely attributed to SDB.[32] The investigators are highly experienced with rigorous pediatric scoring protocols necessary to produce accurate standard SDB measures, as well as more subtle, experimental ones. The PI assisted on the American Academy of Sleep Medicine committee that reviewed pediatric scoring standards and developed the Academy's 2007 Scoring Manual.[62,63] The investigators are funded by the NIH (HL080941) to further develop esophageal pressure and RCREC methods that improve identification of outcome-relevant pediatric SDB. They have already published preliminary data to suggest that esophageal pressures, in contrast to standard sleep study measures, can distinguish post-AT children with and without residual ADHD.[31] The investigators also have shown that RCREC predict sleepiness as well or better than other objective polysomnographic measures, and continue to do so even after the standard apnea / hypopnea index is taken into account.[72,73] The RCREC are derived from a patented computer algorithm (see appendix), invented by the PI and co-investigator Joseph Burns, PhD, at Michigan Technological University. Quantified RCREC reflect the degree to which EEG spectral power in specified frequencies varies in synchrony with non-apneic respiratory cycles during sleep. Published data from the investigators suggest that RCREC reflect subtle but numerous microarousals that are invisible to the human eye,[73] magnified by increased respiratory effort in SDB,[75] and ameliorated by treatment for SDB.[72] Finally, the investigators have also been the first to demonstrate that analysis of sleep dynamics can distinguish children with SDB from normal controls more effectively than do standard polysomnographic measures.[76] The mean lengths of contiguous, specific sleep stage bouts, and especially non-REM stage 2 sleep, are computed from staging files generated by manual scoring. These measures show considerable promise to improve the utility of pediatric polysomnograms.

C10.6 The investigators have extensive experience in CPAP titration and home CPAP use for children. The University of Michigan Sleep Disorders Center is among the largest in the U.S. and is one of only 4 now recognized by the American Academy of Sleep Medicine as a Comprehensive Academic Sleep Program of Distinction. About 4,500 patient visits and 5,500 nocturnal sleep studies are performed annually in 19 modern, well-equipped sleep laboratory beds at two accredited Ann Arbor sites. The Pediatric Sleep Medicine Program, directed by investigator Timothy Hoban, MD, is widely recognized as one of the most active and well-developed. Together with a pediatric pulmonary sleep specialist, a child psychologist, a behavioral / developmental pediatrician, and a dedicated registered nurse, the program evaluates about 450 new children each year for SDB. A sizeable pediatric otolaryngology group evaluates many more children for SDB, and performs about 350 ATs each year in 5-12 year-old children, the large majority for obstructed breathing and especially SDB. As in most of the U.S., virtually none of these children receive follow-up polysomnograms. Only those with clearly persistent post-operative SDB symptoms, or occasional children with particularly severe SDB pre-operatively, receive post-operative polysomnograms as part of their clinical care. Those who do have residual SDB are managed through the Pediatric Sleep Clinic, which regularly follows about 120 such children aged 5-12 years on CPAP. Clinic staff, and especially co-investigator Dawn Dore-Stites, PhD, have extensive experience with strategies to optimize CPAP adherence, as these faculty serve as referral resources for a large medical system when it comes to difficult adherence challenges.

C10.7 Children treated by the investigators with CPAP for residual SDB after surgery usually adhere to treatment and experience clinically significant benefit. An IRB-approved, retrospective chart review was performed for 64 children aged 3-12 years who had received a recent AT, been treated with CPAP thereafter for clinical indications, and then had at least one clinic follow-up within the U-M Pediatric Sleep Program. Among these subjects, 24 (56%) of the boys and 15 (71%) of the girls were obese (with BMI z-scores of at least 1.84 or 1.76, respectively). Among the 43 children (67%) who had been adherent with CPAP for at least 3 months, with adherence defined as ≥ 4 hours of use per night on average, 35 (81%) experienced some significant neurobehavioral improvement as reported by parents to their children's clinicians. Among the 8 children with less, but some regular CPAP use, 4 (50%) were reported to have such benefit. In contrast, among the 13 children who were non-adherent, only 10 (23%) had such benefit ($p<0.0001$ for the difference between children with and without good adherence). Where improvement or lack thereof in specific neurobehavioral benefits had been documented, benefits likely to have arisen because of CPAP included

improvement in sleepiness (86% of adherent subjects, vs. 25% of the non-adherent) and school performance (43% vs. 14%). Adherent children experienced improved mood (78%), attention (58%), and daytime behavior overall (50%), with reduced aggressive behavior (40%), hyperactive behavior (20%), and snoring (92%). These preliminary data are important because they show that CPAP as administered by the investigative team, after AT, is 1) well tolerated by the majority of children (43 of 64); 2) associated with significant clinical improvement beyond that provided by surgery; and 3) likely to cause the improvement, as non-adherent children, a natural if imperfect control group, did not as often experience the same benefits. Furthermore, this clinical sample in the State of Michigan shows high rates of obesity, an important risk factor that makes residual SDB after AT most likely.[26] With one of the highest obesity rates in the U.S. (http://www.cdc.gov/obesity/data/trends.html), Michigan is an ideal setting for the proposed research.

6. Protection of Human Subjects

6.1 Risks to Human Subjects

6.1.a Human Subjects Involvement, Characteristics, and Design: Enrolled human subjects will number 132 and range in age from 5.00 through 12.99 years old at enrollment. Their parents or guardians will likely be young or middle-aged adults. Children will have sleep, behavioral, and cognitive assessments and two-thirds will use continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) for 6 months. The protocol will require several visits to the medical center, and either a) 3 nights and 2 days (total) spent in the sleep laboratory as an outpatient over a 6-month period for the CPAP group, or b) 2 nights and 2 days for the control group. Parents will be interviewed and asked to fill out child sleep and behavior questionnaires. The gender, racial, and ethnic composition of the subject population for all specific aims will resemble a cross-section of the local and surrounding, Southeast Michigan population, as reflected by data from previous NIH-funded pediatric sleep research here and from state-wide figures (see Targeted/Planned Enrollment table). The age range for this study is chosen because 1) the focus is on childhood sleep-disordered breathing (SDB), which is likely to have different etiologies, symptoms, and consequences in adults, 2) children younger than 5 years-old would require different cognitive assessments that would be difficult to synthesize with those of older subjects, 3) children younger than 5 years often take daytime naps, and Multiple Sleep Latency Testing would have less clear validity, 4) teenagers gradually develop adult rather than childhood features of sleep-disordered breathing (SDB), and 5) the frequency of adenotonsillectomy (AT) is greatly reduced in children older than the group to be studied. The health status of the subjects involved in this research will generally be good. At the time of enrollment, subjects will be scheduled to undergo AT on an elective basis within several weeks, based on their otolaryngologists' clinical determination (with or without objective confirmation) that significant SDB is present. Some subjects may also have a history of recurrent or chronic infections as another reason to have AT. Most will be otherwise healthy, as medical and psychiatric conditions that would significantly limit the ability to test the proposed hypotheses will be exclusion criteria.

Specific inclusion criteria will include:

1) Age ≥5.00 and ≤12.99 years at study visit 2, for reasons explained above.
2) Parental ability to speak and read English, for example on behavioral rating scales, which are important measures for this study.
3) Absence of known or anticipated neurological, psychiatric, medical, or social factors likely to invalidate assessments, make adherence with PAP highly unlikely, confound ability to demonstrate improvement with PAP, or make local follow-up at 6 months unfeasible. Some psychiatric conditions may be provoked or exacerbated by SDB, and those most commonly implicated – Attention Deficit/Hyperactivity Disorder, Conduct Disorder, and Oppositional Defiant Disorder – will not be exclusions. However, more pervasive conditions such as severe autism will be excluded.
4) Absence of chronic stimulant, hypnotic, or strongly sedating medication, unless families and their pediatricians are comfortable with 2-week drug holidays before the evaluations at 4 and 10 months after AT. Other chronic medications, in children without anticipated dose changes, will not be exclusions.

After careful consideration, neither specific SDB symptoms, laboratory evidence, nor neurobehavioral comorbidity will be required initially to participate in this research. This will (1) allow participation by subjects with a wide range of SDB symptoms and neurobehavioral comorbidities; (2) facilitate detection of associations between these measures; and (3) avoid dependence on unsubstantiated assumptions as to what particular symptom, laboratory finding, or neurobehavioral deficit is necessary for improvement to occur on PAP. The investigators realize that in practice, some self-selection may enrich the sample with children whose families do have post-AT concerns about SDB symptoms. To avoid the possibility that such participants may be too infrequent, the investigators will assess the proportion of children with positive SDB questionnaire scores (> 0.33 [43]) after each group of 10 subjects has had AT. If this proportion falls below 50%, the investigators will enrich the sample, for example, by requiring every other (i.e., every 2nd) participant to have a high SDB score, at both the initial pre-AT screen and re-assessment 4 months later, before randomization. The proposed research is not epidemiologic, and validity will not suffer from selection bias or artificial enrichment of the sample. The research does test for associations that will depend on wide ranges of requisite variables, but

also on sufficient numbers of post-AT children with residual SDB and comorbidities that may improve with PAP. The current inclusion criteria and contingency plan are likely to permit the most effective tests of the proposed hypotheses.

Recruitment will occur at practices of 9 otolaryngologists who together are estimated to perform 90% of all childhood ATs in Washtenaw County. The investigators have worked with these surgeon groups and their staff for 10 years to recruit pediatric subjects successfully, achieving targeted goals for two other NIH-funded R01 projects. Co-investigator Susan Garetz, MD, a pediatric otolaryngologist and board-certified sleep specialist, will lead recruitment efforts. In the research now proposed, the investigators will establish contact with families and enroll those interested just prior to AT. Most commonly the clinical decision to perform an AT is based on symptoms of obstructed breathing at night, such as loud snoring, restless sleep, snorting with arousals, and perceived consequences. Previous surveys by the investigators have shown that these 9 otolaryngology practices rarely obtain polysomnography prior to scheduling AT for a clinical diagnosis of SDB. This practice closely resembles those of North American otolaryngologists more broadly, who obtain polysomnography in less than 10% of cases prior to AT for SDB.[22]

Contact will be made with subjects before AT (as opposed to 4 months later) for two reasons. First, the investigators would like to minimize decisions not to participate simply because good improvement in symptoms are seen after AT. Although every family will have the right to withdraw at any time from the research, the investigators believe that even children who improve after AT may well improve further with definitive treatment for any residual SDB. Second, the visit just before AT will allow the investigators to administer simple but important questionnaires that will assess SDB symptoms and neurobehavioral morbidity at baseline, before any major intervention in most cases. This could provide important opportunities to explore selection bias at study entry; adjust statistical models for SDB or neurobehavioral problem severity at entry; compare gains from AT to those from subsequent PAP; and perhaps gain insight into what symptoms prior to AT may predict ultimate need for post-surgical PAP that provides additional benefit. Further, this visit will include a very brief cognitive assessment that will give young children experience with a one-on-one testing experience to reduce subsequent novelty and improve reliability. However, an addendum to this protocol also allows enrollment after the child's adenotonsillectomy (at or before study visit 2) for families who are not able to to schedule a preoperative study visit due to time constraints at the time of the initial referral, or because they were referred only after the surgery. This will allow more opportunities for participation of eligible children who would otherwise have enrolled preoperatively.

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Adherence to CPAP or BPAP is also central to the proposed research. The investigators do not wish to set up an adherence-promoting system that would be completely unrealistic in clinical practice, for fear that research results would not be generalizable. Furthermore, hypothesis 2b seeks to compare adherent and non-adherent subjects. However, the protocol does have several features that will facilitate adherence and help to ensure that about 2/3 of participants are in fact adherent to PAP. These features include involvement of an equipment provider (respiratory therapist at MedEquip) who is particularly experienced with PAP for children; regular follow-up by phone and in person with Sue Armstrong, RN (Pediatric Sleep Clinic Nurse) and the study coordinator; and intervention whenever necessary by Dawn Dore-Stites, PhD, a child psychologist and faculty member of the Pediatric Sleep and Behavior Clinic who specializes in desensitization and other behavioral approaches needed to help children and parents adapt to successful use of PAP at home. Approaches that are similar if not quite so thorough (e.g., with weekly contact initially) are routine in our pediatric sleep clinic, as at other leading academic programs, and have resulted in a 67% adherence rate in our preliminary data.

Despite their special vulnerability as research subjects, children are involved in this protocol for compelling reasons. Childhood SDB is a distinct entity from the adult form in many respects, and only study of the appropriate age group will improve understanding and treatment of childhood SDB. Large tonsils most often play an important role in children whereas they rarely do in adults. Adenotonsillectomy for SDB is performed much more commonly in children than adults. Vulnerability to effects of SDB during childhood, in comparison to adulthood, is complicated by rapid development in intellectual, emotional, and physical spheres that could have lifelong impact. Neurobehavioral consequences of SDB arise in both children and adults, but whereas inattention and hyperactivity are often main complaints for families of affected children, adults much more often

focus on daytime sleepiness. Extensive data from adults are already being generated with regard to CPAP, optimal candidates for CPAP, and benefits of CPAP, including neurobehavioral benefits (e.g., see 5 U01 HL068060), whereas neurobehavioral effects of CPAP in children remain largely unexplored.

The proposed protocol adheres to the ethical principles outlined by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[115] Respect for persons is maintained, as the adult parent or guardian with full capacity will provide written informed consent, a child over age 8 or able to understand the study will provide written assent, and a younger child will give verbal assent. The principle of beneficence is respected as for each participant the potential for personal benefit from this study will outweigh the small risks involved. This study will not subject any child to tests or treatments that stand no chance to benefit him or her personally. This follows from decisions made about the randomized control arm (see Introduction), which will involve only standard care and periodic contacts from investigators. No child will be deprived of needed medical care. Agreement to participate in this research will not prevent any family from withdrawing at any time. Although control subjects will receive no intervention beyond frequent contacts with investigators or the program manager, the investigators anticipate based on their previous research that few will leave the protocol to seek clinical care. Those contacts also will be used to ensure that any highly unlikely but conceivable situations in which absence of CPAP could pose an urgent medical threat will be detected early so that the subject can be removed from the study. Lastly, the principle of justice is respected because the population to be studied will be exactly that which stands to gain most from the results of the study.

For the CPAP group, the dose, frequency, and administration of PAP after AT will follow standard clinical care approaches. Use of the PAP machine will be encouraged for every night and whenever sleep occurs during the day. The pressure setting will be determined in a sleep laboratory during a standard CPAP (or BPAP, when necessary) titration study. Titrations will start at 4 cm of water pressure, a minimal amount necessary to counter-act the effects of breathing through the mask and tubing, and provide a slight splinting effect for the upper airway. Sleep technologists experienced with children, in a control room adjacent to the sleep laboratory bedroom, will increase pressure settings in small increments until they see no residual evidence of SDB. If CPAP settings become too high, CPAP is not tolerated even at lower settings, CPAP is not effective, or hypoventilation persists, BPAP may be tried and titrated in a similar manner. After scoring by technologists, Timothy Hoban, MD (director of the Pediatric Sleep Medicine Program and board certified in sleep medicine) will review the entire recording and determine an optimal pressure setting. Requests for this setting, and equipment that proved effective in the sleep laboratory, will then be sent to MedEquip, where an experienced respiratory therapist will distribute the equipment to families and educate them on how to use it.

The proposed clinical research will occur at one site (University of Michigan Health System). Another site, Michigan Tech Research Institute (an Ann Arbor unit of Michigan Technological University) will perform signal analysis on de-identified recordings. Otolaryngologists at the University of Michigan and St. Joseph Mercy Hospital, also in Ann Arbor, will assist with identification of subjects and families willing to hear more about the protocol, and will forward contact information to the investigators on a FAX form. This form, in use for the past 11 years, contains minimal information about the scheduled surgery, and a brief signed parental consent for investigators to call back to discuss the study. No identifiable data will be sent from the investigators to St. Joseph Mercy Hospital, except in the rare instance in which urgent health information has been uncovered in the course of the research. The protocol then calls for prompt notification of the subject's otolaryngologist, with permission of the parents. This IRB-approved system has worked well in practice for many years.

6.1.b Sources of Materials: Research material will be obtained from questionnaires, interviews, parental behavior rating scales, neuropsychological tests, nocturnal polysomnography, and daytime Multiple Sleep Latency Tests. All of these data will be obtained specifically for research purposes. Access to medical records will be requested from the University of Michigan Medical IRB, mainly for any demographic data, medication lists, or other information that might be missing from study-specific forms, and not for collection of any of the main variables under study. Each of the investigators will have access to individually identifiable private information about human subjects. Individuals not on the investigative team will not have access to this information. Written data will be stored in locked cabinets, in locked offices, separate from keys that identify subject names. Electronic data will be stored on password-protected, regularly-backed-up server files and on DVDs or external hard drives kept securely.

6.1.c Potential Risks: Only minimal risks are associated with the interviews, behavioral ratings, and neuropsychological tests to be administered to children or their parents. Neuropsychological testing will be brief, about 2 hours in total, but could induce some fatigue. Children who have difficulty with the tests could experience some level of anxiety. Results of testing could in some cases engender parental concern. Similarly, risks associated with sleep tests are relatively small. In preparation for polysomnography, particularly for the first time, placement of the esophageal catheter down the nose and throat can create transient discomfort or anxiety for some children. Vomiting, persistent coughing, or nose bleeding occur rarely. Other risks of the sleep studies include the stress of an unfamiliar environment, stranger anxieties, separation anxieties (e.g., during daytime nap studies), a night of sleep that may not be as restful as that obtained at home, and cutaneous allergic reaction or irritation that can occur at the site of electrode or tape placement. Finally, as in any research, risks exist for breach of confidentiality and loss of data. Overall, the benefit to the child of sleep study results, neurobehavioral assessment, and what is almost always a fun, positive, and memorable experience is likely to outweigh potential harm. Almost all children and families (95%) who have completed similar testing protocols at baseline in the past have been glad to repeat them again one year later.

The protocol also calls for 2/3 of the subjects to use CPAP or BPAP nightly for 6 months. This requires commitment on the part of each child and parent. However, the treatment is not onerous, and in clinical settings CPAP has been used for many years in children of all ages.[47] The treatment is considered safe and effective in children[47], however, PAP devices, most masks, and equipment are not yet FDA-approved for use in children. In adults with sleep apnea, use of CPAP improves quality of life to an extent that substantially outweighs any detriment arising from having to use the equipment.[116] Randomized controlled CPAP trials now commonly use sham CPAP or no CPAP as a control, even in vulnerable or gravely ill populations such as patients with amyotrophic lateral sclerosis, heart failure, epilepsy, or stroke.[117,118] The research now proposed will include a "No CPAP" comparison group. However, children who are identified as having excessively severe OSA at study visit 2, to the point that the investigators do not have equipoise with randomizing them to PAP or no PAP groups, will be withdrawn from the study and referred to clinical care before randomization. Surgical and orthodontic alternatives to PAP, after AT in children, are neither well-studied nor widely available. Although non-steroidal anti-inflammatory or steroid medications may be of some use in children with the most mild sleep-disordered breathing,[119] these agents are not universally effective, may fail particularly in more severe cases of residual sleep apnea, and can carry their own risks. The large majority of children who have AT at the University of Michigan or St. Joseph/Mercy Hospital receive no SDB-specific testing or treatment after their surgical procedure, so the control subjects will not lack intervention they would otherwise receive. Like all subjects outside this research protocol, they will have the option to pursue any evaluation or intervention they would like outside the research protocol.

Specific risks from using PAP include mask discomfort or irritation of the face. Nasal congestion or mouth dryness can arise from mouth leaks when a nasal mask is used. Embarrassment at having to use PAP, especially if observed by peers, could be another risk, especially for older children. These risks are not generally considered serious, though they need to be addressed to optimize PAP adherence. Rare but more serious consequences can conceivably include infection or changes in pigmentation at a persistently irritated site on the face (e.g., the bridge of the nose) or limitation of mid-facial growth during the period when the mask is used. Mid-facial growth retardation[57] in particular is highly unlikely in the proposed protocol, which requires use of the mask for only 6 months.[52] There have also been rare reports of a pneumothorax associated with PAP use, aspiration of vomit from a PAP mask by a severely developmentally delayed, disabled child, and death of a disabled child who became entangled in the PAP tubing.

6.2 Adequacy of Protection Against Risks

6.2.a Recruitment and Informed Consent: Potential subjects and their parents or guardians will first hear about the study from their pediatric otolaryngologists and associated office staff, at the time that the surgery is scheduled. A parent or guardian willing to hear more about the study will sign a brief consent, and on the same one-page form provide (in conjunction with the otolaryngologist) simple information about contact numbers, date of surgery, reason for surgery, symptoms of SDB, and likelihood of SDB. The form will be faxed to the investigators. Alternatively, parents of potentially eligible subjects may learn about the study from the study brochure provided to patients or the ClinicalTrials.gov posting. They may then request contact by a member of the study team. An investigator will call the parents to explain that:

- We are conducting a study on sleep disorders, behavior, and thinking in children who have AT for SDB;
- We believe a good number of children with SDB may be affected in these areas;
- Participation in the research will require either 2 or 3 separate overnight stays in the Sleep Laboratory;
- Some compensation to both parent and child will be provided for their time and effort;
- Some children (2/3) will be randomly assigned to use PAP at home nightly for 6 months, starting 4 months after AT; other children (1/3) will use no PAP during the same period;
- All data collected will be kept confidential;
- All participants are free to withdraw from the study at any time;
- Summary test results will be provided upon request within several months after final testing, when scored neuropsychology and sleep results from initial and follow-up sessions are ready;
- If preliminary review of test results suggests that something may need urgent medical attention, these findings will be communicated promptly to the family and treating surgeon.

During this initial phone call, data also will be gathered to ensure that the subject meets inclusion and exclusion criteria. Potential participants and their families will be invited to the Sleep Disorders Center to further review the above points, hear about the research protocol in more depth, tour the sleep rooms, see the equipment used during sleep studies, and see sample PAP equipment. At this time, a study team member will obtain signed permission / consent from a parent or guardian and assent from the child. Children older than 8 years or able to understand the nature of the research will be asked to sign assent; other children will be asked for verbal assent. One copy of the documents will be placed in the subject's medical record, one given to the parent, and one kept on file by Dr. Ruzicka.

6.2.b Protection Against Risk: Fatigue and anxiety during cognitive testing will be minimized by a neuropsychology technician who has extensive experience with children and will give breaks from testing as needed. If results of behavioral or cognitive assessments engender parental concern, the child and parents will be invited back to a meeting with a child psychologist co-investigator, who will discuss the findings in an appropriate manner and review options for further evaluation or treatment outside the research protocol. Prior to study enrollment, tours of the sleep laboratory will give subjects and families a preview of that environment and equipment used there, reduce any possible fears or anxieties, and give them a good understanding of study requirements in relation to family, school, and job commitments. Technicians experienced with children and anxieties of this age group will conduct sleep studies. Children will be offered a topical anesthetic prior to insertion of the esophageal pressure catheter. However, children who do not tolerate placement of the esophageal catheter (anticipated based on this group's past work to constitute a minority of these volunteer subjects[68]) or other equipment will not be required to use them. Parents will stay with children during overnight testing to reduce separation anxiety. Spacious pediatric sleep rooms are designed to include a separate bed for the parent. We will instruct subjects who obtain poor sleep in the laboratory to avoid operating dangerous toys, bicycles, and machinery until adequate sleep is recovered. We will also ask parents to supervise such children at home until restorative sleep is obtained. During sleep studies, a physician investigator will always be on call for any unexpected emergencies. Studies will be performed at the Sleep Disorders Center in the 10-bed Michael S. Aldrich Sleep Disorders Laboratory, where a 24-hour technical staff including pediatric and research technologist pods is well prepared to meet the needs of children and families who participate in research. If a cutaneous reaction to electrode placement occurs, technicians will remove the electrode and reapply it at another site with a different type of adhesive. Mild skin irritation will be treated with topical creams as needed. Moderate reactions at multiple sites, or any severe reaction, will warrant study termination. Finally, every effort will be made to ensure, as in the investigators' past NIH-funded pediatric sleep protocols, that this research experience is fun, positive, and rewarding for each subject and family.

Problems with PAP use will be preempted in part by thorough education of parents, and children, about the purpose, potential benefits, and importance of nightly adherence. Participating families will be well educated about potential problems, and what to do about them, even before starting PAP. The PI has some of the earliest published experience with strategies to optimize CPAP adherence,[120] and the investigators are thoroughly familiar with application of this therapy to children. Best efforts will be made first in the sleep lab, just prior to the CPAP titration study, and again at the visit to the durable medical equipment company, to make sure each child is optimally fitted for a CPAP interface (generally a nasal mask, though sometimes a face mask or nasal pillows). This will minimize risk for discomfort or irritation.

After PAP is initiated, contact initially with investigators will occur weekly (at least by phone) and will provide multiple opportunities to detect poor fit before this could lead to serious irritation, wound, or infection. Mask discomfort will be addressed as soon as it is apparent by re-adjustment of headgear straps, or trials of different mask models. Nasal congestion or mouth dryness, depending on the apparent cause, will be ameliorated by reducing any mouth leak (e.g., by using a chinstrap); use of a full face mask; nasal saline irrigation; or improved use of heated humidification. Use of PAP on every night will be encouraged: parents and children will be educated about its importance, what can happen if PAP is not used, and also the fact that an occasional night off PAP could have some consequence – but not enough to make an occasional exception (e.g., for a "sleep over" at a friend's house) impossible. The concern that long-term use of a PAP mask could diminish growth of the mid-face will be broached, but presented as most unlikely to occur within a 6-month protocol.

Some children in this protocol will use PAP without having enough underlying, residual SDB to benefit from the intervention. During the treatment trial, neither investigators nor families will know who these children are. Although symptoms may be readily apparent, sleep study results will not be available until after study participation is complete, for several reasons. One is that sleep studies are to be scored in batches -- with several subjects' pre-PAP and post-PAP studies all in the same de-identified batch -- to avoid any influence of scoring drift over time. A second reason is that at present, knowledge about how post-AT care should be guided by sleep study results remains quite limited. The research now proposed, in fact, aims in large part to address this void.

Fortunately, subjects without residual SDB after AT, as compared to subjects with SDB, have no known additional risks to use of PAP. When the PAP titration studies are performed, children without SDB will have normal breathing, technologists will have no reason to test more than the lowest CPAP settings, and the reviewing physician (co-investigator Timothy Hoban, MD) can be expected to assign the lowest settings for use at home. In other studies of adults, even CPAP at fixed pressure settings for all research subjects, whether healthy or ill, has been safe whether SDB is present or absent.[121-123]

Families whose children have been randomized to the control group will be contacted by the program manager during the 6-month trial at intervals designed to replicate the frequency of investigator contacts in the CPAP group. Discussion will focus on recuperation after AT, general health, and also any suggestion of serious adverse effects that would warrant discontinuation of study participation and referral for clinical evaluation. These end-points would include recommendation by a child's pediatrician or otolaryngologist to pursue this option; development of a new, serious cardiopulmonary condition that makes prompt assessment and treatment for any residual SDB imperative; or emergence of serious academic or developmental concerns in the setting of obvious, persistent symptoms of SDB. Each questionable case will be brought by the program manager to the PI and, depending on the nature of the event as outlined in the Data and Safety Management Plan, the DSMB(section 6.5 below) for a decision.

All information collected in the course of this protocol will be treated confidentially. Written authorization will be obtained from a parent or guardian prior to release of any study results, except in the rare case of emergent findings that require immediate attention of a child's clinician. Applicable IRB, privacy office, and contract office approvals will be obtained prior to transfer of data outside the research team. Printed data will be stored in locked cabinets within a locked private office of the program manager. Data will be linkable to subject names only by a key kept separately from the data files. Computer data will be password-protected, accessible only by study personnel, and backed-up to prevent accidental loss. Published reports will not include names or make individual participants readily identifiable in other ways. These precautions are highly likely to maintain confidentiality effectively.

Any unforeseen urgent medical problems that arise during testing will be handled or triaged by the physician investigator on call and the technologists at the Aldrich Sleep Laboratory. This fully accredited facility studies about 5 children every night of the week for clinical or research purposes. Standard protocols are known by the technologists and readily available for emergencies such as fire, threatening arrhythmia, or seizure. Data and safety monitoring for this non-randomized clinical trial will proceed as outlined below.

6.3 Potential Benefits of the Proposed Research to Human Subjects and Others

Each subject has a significant chance of substantive benefit, at comparatively low risk and expense. Each child will benefit by 1) free testing for residual, post-AT SDB; 2) family knowledge, if desired, of any residual SDB after the clinical trial is completed, to facilitate decisions about ongoing care thereafter; 3) identification of potentially treatable behavioral or cognitive problems that may not have been suspected or diagnosed in the past; 4) participation in research that past subjects and families have often found to be an enjoyable, educational, and rewarding experience; 5) development of positive attitudes toward clinical research and ability to serve as community liaisons who can raise awareness of SDB among other families and children at risk. In addition, families whose child has been randomized to the CPAP group may benefit from the free, gold-standard treatment for any possible residual SDB, with careful expert attention to PAP adherence for the duration of the trial. After families have completed the protocol, those from CPAP and control groups will be assisted with referrals for any sleep, behavioral, or mental health care that they would like to pursue. Children whose families and pediatricians would like them to remain on PAP will be able to keep the PAP equipment at no cost, which could be an important opportunity in some instances. The CPAP machines that will not continue to be used by CPAP group subjects will be returned to the investigators. These units will be made available to any control families who, with assistance from their child's physician, wish to use CPAP for clinical purposes after completion of the research protocol.

Potential benefits to other children of the data to be obtained in this study are significant. The long-term risks to sleep, health, cognition, and behavior of unrecognized and incompletely treated SDB after AT could be substantial. Diagnosis and treatment of residual SDB after AT – now believed to occur in half or more of operated children – could have significant impact on social, intellectual, monetary, and health-related spheres not only during childhood but into adulthood as well. Risks to the subject from this protocol are not more than "minor over minimal," as described above. Therefore, the risk:benefit ratio for children who participate in this study and parents who assist them is excellent.

6.4 Importance of the Knowledge to be Gained

For society, the potential benefits are sizable. Sleep-disordered breathing has high prevalence among children (at least 2-3%) and is most commonly treated by AT. However, current data, perhaps in part because of increased childhood obesity, suggest that many children still have some residual SDB after the procedure is performed. This research will begin to clarify which methods best identify appropriate candidates for additional SDB treatment after AT, and what benefits can be expected from PAP in this setting. This research will provide some of the first data directly relevant to common clinical decisions – who to evaluate and who to treat further after AT – that at present must be made based largely on published pre-operative data that may not pertain. The potential impact of knowledge from this study will therefore be substantial, both in terms of improved health outcomes and reduced societal and healthcare costs for children with incompletely treated SDB. Risks of this research arise from testing procedures (neurobehavioral and sleep) that are commonly performed in children and generally rated as "minor over minimal risk" at most. Risks also arise from treatment with PAP, but this is not a systemic medication, remains non-invasive, and has overall an extremely favorable side-effect profile and safety record in children as in adults. Finally, risks may arise from randomization of some children to receive no PAP. However, in standard care the vast majority of children who have AT are offered no follow-up testing or treatment. In this protocol, all children will receive follow-up testing, and treatment will still be available outside the research protocol to any subject whose family decides to seek treatment as part of their standard clinical care. Therefore, risks for this study seem highly reasonable in relation to knowledge to be gained. No test article is to be used in this research.

6.5 Data and Safety Monitoring Plan

The goal of the data and safety monitoring plan (DSMP) will be to protect patient safety and ensure the integrity and validity of the data. We will achieve this with a protocol designed to monitor and report adverse events specifically related to the protocol evaluations and PAP treatment, monitor study progress, assess appropriateness of continuing or stopping the trial, ensure protocol compliance and data accuracy, and prevent biased interpretation of data or conflict of interest. We will register this trial in a clinical trial registry that meets

NIH approval. We will elaborate and modify this DSMP as necessary in working with the NIH to formulate acceptable approaches.

The original protocol was submitted to NIH and approved for funding with a medical monitor to oversee participant safety and data integrity. But, more recent discussions with the NIH program officer have led to the suggestion that this project may be better served by a data and safety monitoring board. Plans for a DSMB have not been elaborated in detail:

Data and safety monitoring for this randomized, controlled, single-site clinical trial comparing CPAP treatment to no CPAP treatment after adenotonsillectomy will be accomplished in part by a Data and Safety Monitoring Board (DSMB). The board will be composed of individuals with expertise relevant to this study, its participants, or the evaluations and interventions that are planned. The DSMB board members will be external to the investigators, external to the University of Michigan, and otherwise uninvolved in this research. The DSMB will be assembled and guided with assistance from the relevant Program Officer at the NIH. The DSMB will convene, at least annually, and generally by phone, to review and make recommendations regarding recruitment and retention, adverse events, any treatment safety concerns, and data quality or integrity. The Principal Investigator will review, grade, and report any adverse events, ORIOs, or unanticipated problems, with the assistance of the Program Manager, to the IRBMED, the DSMB, and the NIH program officer as required by the approved study-specific DSMP.

Adverse Events

The Principal Investigator will review and assess adverse events for nature, seriousness, severity, frequency, expectedness, and relatedness to the study interventions. Information on adverse events or other significant reportable occurrences on this protocol will be reported to the Data Safety Monitoring Board. The DSMB will be responsible for (1) periodic review and evaluation of participant safety, recruitment and retention, and study conduct, and for (2) recommendations for continuation, modification, or termination of this clinical trial. The DSMB will be notified of project-related, medical or psychological conditions, or adverse events that may require intervention. Protections against risks in the proposed research will include those detailed above (section 6.2.b). No new intervention, device, or drug is to be studied in this protocol, and risks are likely to be considered by the IRB as “minor over minimal,” as in the past for other pediatric sleep research studies at the University of Michigan. The PAP equipment used in the treatment arm of this clinical trial is commercially available (by prescription) and commonly used for adults and children with SDB, though PAP is not specifically FDA-approved for use in children.

Adverse consequences related to sleep studies, cognitive testing, PAP treatment, or lack of PAP will be communicated by the Principal Investigator to the IRB and the DSMB, either individually or in aggregate reports, depending on the nature, frequency, severity, and seriousness of the event. The investigators will follow an approved study-specific IRB reporting plan for expected and unexpected adverse events, serious adverse events, and unanticipated problems. The PI, IRB, and the DSMB will be responsible for monitoring the safety of the study. The PI will characterize the nature and grade of the adverse event. Non-serious expected adverse events that may be reasonably anticipated to arise as a result of study procedures will be described in the consent form, recorded in practice, and reported to the IRB annually as part of the progress report. SAEs and UaPs related to the study will be reported within 7 days to the IRB, DSMB, and NHLBI program officer per the study-specific reporting plan (see the Data and Safety Management Plan) . The PI or designee will notify the DSMB chair and NHLBI program officer about the occurrence of a SAE related to the study or any death regardless of attribution within 24-48 hours of the PI being notified of the occurrence. Non-serious, expected adverse events that occur with greater than anticipated frequency or severity will be reported to the IRB; consent forms will be modified as necessary; and subjects already enrolled will be advised accordingly. Unexpected, nonserious adverse events that are moderate to severe and related to the protocol will be reported to the IRB and DSMB within 14 days and to the NHLBI program officer within 30 day if the events are unanticipated problems. An expected but serious adverse event that is related to study interventions will trigger notification of the IRB, DSMB, and NIH program officer within 7 days of the event, or within 7 days of the date that the study team is notified of the event. Nonserious unanticipated problems or device effects will be reported to the IRB, DSMB and program officer within 14 days of study team awareness of the safety issue. Intercurrent events and adverse events that are nonserious and expected or not related to

the study interventions (for example, common childhood illnesses, peri- or post-operative events or sequelae) will not be reported with the exception of a subject death which will be reported in expedited manner regardless of attribution. Participating families will receive written directions and encouragement to contact an appropriate physician or nurse at any time, 24 hours per day, 7 days per week, about any medical concern or adverse event related to the research study. In addition, frequent phone and face-to-face contacts, as described in section C6 of the research strategy, will be maintained with each family during the clinical trial.

An adverse event log will be maintained by the Program Manager. The Program Manager will meet weekly with the PI to review study progress, any protocol deviations, and resolution of adverse events. The project and consent forms will be reviewed at least once each year by the IRB. The investigators will prepare a full report annually for the DSMB to summarize adverse events, responses of the investigators, and any changes to the protocol or consent and regulatory documentation.

Data Monitoring

The annual report from the investigators to the DSMB will include summaries of enrollment, subject withdrawals, and numbers of subjects who have completed the protocol. Any problems with data collection, quality, analysis, management, loss, or confidentiality will be described, along with any consequent protocol changes and options still available to remedy the concerns. Interim data analysis, to assess appropriateness of trial completion, is not anticipated. This early stage clinical trial involves extensive study, among 120 participants, of many variables to be examined in this setting for the first time. Completion of the trial will provide key initial insight into a range of variables that warrant assessment even if other variables prove informative with fewer than 120 subjects. Risks of PAP are small, potential benefits are large, and harm to participants from completion of the trial with the full sample size is not anticipated.

DSMB Reports

The DSMB will complete annual reports indicating: a) approval that the study retains acceptable safety and data validity; b) approval contingent on specified modification to existing protocols; or c) disapproval for continuation based on safety concerns that cannot adequately be addressed, or threats to validity of the data sufficient to warrant closure of the study.

If the PI disagrees with recommendations to modify or terminate the study, the DSMB Chair, IRB, and NIH will be notified in writing about the disagreement and the reasons for it. The PI, DSMB Chair, and designated NIH official will be responsible for reaching a mutually acceptable decision regarding the recommendations.

6.6 ClinicalTrials.gov

This application includes an applicable clinical trial that requires registration in ClinicalTrials.gov. The PI, unless informed otherwise by the NIH, will be responsible for registering the trial before it begins.

7. Inclusion of Women and Minorities

The proposed study population – children with SDB – is composed of approximately equal numbers of boys and girls, perhaps with a slight preponderance of boys.[1] The sex/gender distribution within the proposed research sample should reflect this broader population distribution. Boys and girls will be recruited for this study irrespective of gender. Some evidence suggests that the association between SDB and daytime behavioral problems may be more prominent in boys than in girls,[9] but not to an extent that would warrant exclusion of girls from the research. Children will be enrolled in year 1 through the beginning of year 4 of this project. Another NIH-funded protocol by the investigators, focused on sleep apnea in children undergoing AT between 2005 and 2009, enrolled only slightly more boys than girls within a sample of n = 140. Therefore, no outreach plans are anticipated to be necessary to recruit either gender in the research now proposed. The sample composition should resemble that shown in the Targeted/Planned Enrollment table, extrapolated from data on (1) children undergoing AT at this institution from 2006-2009, (2) children (n > 1000) referred to the PI's previous NIH-funded research protocols by the same two Ann Arbor otolaryngology groups that will identify potential subjects for the research now proposed, and (3) State of Michigan 2008-2009 health services.

Similarly, SDB affects children of all races and ethnicities. Some studies suggest excess frequency of SDB among African American children,[124] but no studies suggest race or ethnicity-based differences in effects of SDB on cognition, behavior, or daytime sleepiness, the neurobehavioral outcome variables for this protocol. No data or plausible physiology suggest differential response of SDB to PAP among different races or ethnicities. Therefore, recruitment for the proposed research will proceed without plans to select or exclude any given race or ethnicity.

In the Targeted/Planned Enrollment table, some races or ethnicities are not highly represented because the overall sample size for subjects who complete the protocol is only n = 120; the geographical location of the study encompasses only limited numbers for some of these minority groups; and otolaryngology practices where subjects will be identified already account for an estimated 90% of all adenotonsillectomies (defining eligibility for the study) in a large geographic area (Washtenaw County, population 347,000).

9. Inclusion of Children

The proposed study will enroll only children, who must be between 5.00 and 12.99 years old at study entry. These ages represent a period at which several of the outcomes central to this study, such as inattention, hyperactivity, and disruptive behavior, are particularly prominent problems. Optimal cognitive functioning, behavior, and alertness are critical to rapid learning and normal development. In children less than 5 years old, assessment of cognitive function would require different instruments (and generate different data) than those that can be used starting at age 5. Hyperactivity could be more difficult to distinguish from normal behavior. In addition, performance of the Multiple Sleep Latency Test to assess daytime sleepiness becomes increasingly difficult in children under 5 years, many of whom still take regular daytime naps. Above age 12, AT is increasingly rare, and morbidity due to SDB is more likely to show an adult pattern with overt daytime sleepiness but little or no hyperactivity.[64]

The investigative team has considerable experience working with children between 5.00 and 12.99 years old. Most of the investigative team involved with the proposed research also worked together on 1, 2, or 3 previously funded NIH awards that focused on SDB in children within the same age range. This includes Dr. Giordani, a neuropsychologist particularly experienced in pediatric research; Dr. Garetz, a faculty member of the Division of Pediatric Otolaryngology; Dr. Hoban, who directs the Pediatric Sleep Program; Dr. Ruzicka, a program manager who has coordinated or managed NIH-funded pediatric SDB research for 11 years; Mr. Guire, a statistician who has assisted with pediatric sleep research for more than 10 years; and Ms. Fetterolf, an experienced polysomnographic technologist. The sleep studies will be performed in the Michael S. Aldrich Sleep Disorders Laboratory, a 10-bed, fully accredited facility where pediatric and research pods of interested, committed technologists will be available to assist subjects and families who participate in the proposed research. This facility is ideal for children's sleep research protocols. Rooms are large enough to accommodate comfortably a parent who spends the night with the child. Sufficient numbers of children are included in this study to provide a meaningful analysis, as explained in section C8 of the Research Strategy.

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