Official Title: Use of Sleep Endoscopy to Predict Outcomes of Pediatric Adenotonsillectomy

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I. Title

Use of Sleep Endoscopy to Predict Outcomes of Pediatric Adenotonsillectomy

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IV. Purpose of Study

The purpose of this study is to determine whether sleep endoscopy performed in high-risk pediatric patients with obstructive sleep apnea (OSA) at the time of adenotonsillectomy (AT) can predict whether the AT will be successful as an initial treatment for OSA. We hypothesize that patients with multiple sites of obstruction in addition to adenotonsillar hypertrophy (e.g. the nasal airway, velum, base of tongue, supraglottis) will be more likely to have residual sleep apnea on postoperative sleep testing.

V. Background and Significance

Pediatric Obstructive Sleep Apnea Syndrome, Health Care Utilization, and Adenotonsillectomy: Obstructive sleep apnea syndrome OSAS is defined as the symptomatic repetitive obstruction of the upper airway during sleep and has been estimated to affect 1-6% of the general pediatric population.[1-3] Untreated OSAS in children has been associated with childhood hypertension,[4,5] autonomic dysfunction,[6,7] attention deficit/hyperactivity disorder,[8,9] neurobehavioral impairment, [8, 10-13] and poor quality of life.[14-16] These sequelae contribute to a 226% increase in health care utilization among children with OSAS compared to controls, primarily in the form of increased hospitalizations, emergency department visits, and medication use.[17,18] Adenotonsillar hypertrophy is considered the most common risk factor for OSAS in children, therefore unlike in adult OSAS, adenotonsillectomy (AT) is the recommended first line treatment.[19] In large part due to the increasing awareness and diagnosis of pediatric OSAS, the incidence of AT increased dramatically from 1980 to 2005.[20] With more than 500,000 procedures performed per year, AT is now the second-most common procedure performed in children in the US, and 77% of these have OSAS as the primary indication.[20, 21]

Persistent Obstructive Sleep Apnea Syndrome after Adenotonsillectomy: Current guidelines recommend AT as a first line treatment for pediatric OSAS even for those

patients who may have significant risk of post-AT OSAS.[19, 22] Estimates of the prevalence of persistent OSAS after AT vary widely due to use of different polysomnographic criteria for diagnosis. Studies that assessed the risk of post-AT OSAS using a conservative adult threshold for diagnosis demonstrated that even with this high threshold at least 13-29% of children undergoing AT for pediatric OSAS will have significant residual disease[23-25] and approximately 75% of children will fail to achieve normalization on polysomnography.[25, 26] Specific populations of patients that have been recognized to be particularly at risk for post-AT OSAS include those with severe baseline OSAS,[23, 25-27] Down syndrome,[28] obesity,[26, 29-32] and age > 7 years.[26] In obese patients, the prevalence of post-AT OSAS has been reported as high as 73-88%.[30, 33] Since obesity has tripled over the last three decades and now affects approximately 8% of children aged 2-5 years, 18% of children aged 6-11 and 21% of adolescents aged 12-19 years,[34] the problem of persistent OSAS after AT is likely to continue to grow.

No Reliable Method to Identify Patients Who Will Benefit Most from Adenotonsillectomy: Even within populations at risk for AT failure, there is a wide variation in treatment response. One study of morbidly obese children undergoing AT demonstrated only a 37% cure rate while 53% had sufficient residual OSAS to require further treatment with continuous positive airway pressure (CPAP). However, no significant baseline differences were identified between surgical responders and non-responders.[33] The mechanism for failure in this population is unclear, but it is presumed that increased generalized adiposity leads to multilevel obstruction similar to obese adults, thus decreasing the likelihood of success with AT.[30] Similarly a poor but still variable response to AT was observed in children with Down syndrome with post-AT success varying between 18% and 55% depending on the specific criteria used.[35, 36] There are no studies that have clearly identified predictors of AT outcome within the Down syndrome population, however, some studies of Down syndrome patients who failed AT have suggested that multilevel obstruction is common.[37, 38] Thus, although specific populations of patients are known to have greater risk of post-AT OSAS on average, the individual characteristics causing persistent disease remain unclear. Accurate prognostication of the risk of residual OSA after AT for any individual patient remains a challenge. Studies of patients with persistent post-AT OSAS have suggested that multilevel obstruction at locations besides the tonsils or adenoids are likely contributors, but this has not been clearly demonstrated. In this study, we present a novel concept for building a composite model to predict the outcome of AT in children with OSAS. This model will include not just baseline features of history and physical exam but also the findings of dynamic sleep-related collapse at specific anatomic sites in the pharynx observed during sleep endoscopy. This model will give further insight into the mechanisms of airway obstruction as well as the possible reasons for persistent OSAS after AT.

Standardized Approach to Drug Induced Sleep Endoscopy in Children: Kezarian et al have previously described a rating scale for DISE in an attempt to standardize the reporting of endoscopic findings in adults with OSAS.[39] This rating scale evaluates the degree and pattern of obstruction at four levels of the pharynx: the Velum (soft palate), Oropharynx (including the tonsils), Tongue base, and Epiglottis (VOTE). The VOTE rating scale has been demonstrated to have moderate to substantial inter-rater reliability with kappa values

ranging from 0.4-0.8 depending on the specific structures being compared.[40] Other investigators have utilized modified versions of the VOTE rating scale in children, including other levels of the airway such as the nasal airway, nasopharynx, and supraglottis.[41, 42] One recent study demonstrated that sleep endoscopy findings in children were more reliable than during awake endoscopy and noted a strong correlation between polysomnography results and the overall impression of OSA severity during endoscopy.[43]

Dexmedetomidine, which will be used in this study, is a highly selective α_2-adrenoceptor agonist that has been demonstrated to result in a sedated sleep similar to natural sleep without causing respiratory depression[44]. Though there have been some reports of transient bradycardia and blood pressure changes in response to dexmedetomidine infusion (usually transient hypotension of 10% with slow infusion) these cardiovascular effects are mitigated by co-administration of a bolus of ketamine as described in more detail in the Methods section.[45]

Preliminary Data: In a preliminary retrospective review of our patient population and surgical volume, we examined the electronic medical record of all patients who underwent AT over a 12 month period. 498 patients were identified, operated on by the four pediatric otolaryngologists in the group at that time. Approximately 200 (40%) of these were performed for OSAS in patients that could be considered high risk for residual post-AT OSAS and would meet inclusion/exclusion criteria described below. Further retrospective review of patients who also underwent DISE at the time of AT with recorded videos available for review identified 20 patients, 10 of whom also had preoperative polysomnography data available. Among these patients, those who had at least one site of complete obstruction noted during sleep endoscopy had more severe OSAS than those with only partial obstruction (mean apnea-hypopnea index [AHI] 20.9 SD 26.9 vs 8.3 SD 9.8 ($p = 0.3$, Mann-Whitney test). While this preliminary data does not indicate a statistically significant difference in mean baseline AHI, this is based on a very small sample size, thus it is possible that with a larger sample size, this large difference would become statistically significant.

Further Research Needed: Untreated OSA in children has been associated with childhood hypertension, autonomic dysfunction, attention-deficit/hyperactivity disorder, poor school performance, and poor quality of life. These sequelae contribute to a 226% increase in health care utilization among children with OSA compared to controls. Residual OSA after AT in the pediatric population remains a serious concern; as the patient grows and changes, their airway physiology also changes. Although there is a growing body of research suggesting demographic and comorbidity risk factors for post-AT residual OSA, the ability to accurately predict the likelihood or severity of residual OSA for any given individual remains elusive. Possible tools for the evaluation of post-AT OSA in pediatric populations include radiologic examinations, cine MRI scanning, and endoscopic evaluation, along with polysomnography, validated questionnaires, and physical examinations. Determining what instruments best predict residual OSA after surgical intervention is an important step towards more effective OSA management.

VI. Methods

Study Design: This will be a prospective cohort study of pediatric OSAS patients who are considered high risk for having residual OSAS after AT. **This study does not involve any experimental procedures or medication.**

Specific Aim 1: Propose a sleep endoscopy rating scale and evaluate its reliability and correlation with baseline OSA.
Hypothesis 1: In pediatric OSA patients undergoing AT, compared to patients with only partial obstruction, patients with complete obstruction at one or more anatomic sites will be more strongly correlated with worse 1) polysomnography parameters, 2) quality of life, and 3) executive functioning.

Specific Aim 2: Determine associations between a proposed sleep endoscopy rating scale and the outcomes of AT.
Hypothesis 2: In pediatric OSA patients undergoing AT, compared to patients with obstruction only at the tonsils or adenoids, patients with complete obstruction at other sites will show a greater risk of post AT OSA and decreased improvement from baseline with respect to 1) polysomnography parameters, 2) quality of life, and 3) executive functioning.

Specific Aim 3: Develop and validate a composite predictive model of the outcomes of AT including the proposed sleep endoscopy rating scale, demographic variables, comorbidities, and physical exam.
Hypothesis 3: A composite model including a sleep endoscopy rating scale and other preoperative risk factors will be predictive of the risk of residual OSA after AT.

Subjects:
Inclusion criteria: Patients with OSA demonstrated by polysomnography (AHI ≥ 2 or obstructive apnea index ≥ 1) aged 2-18 years who are candidates for AT and **also satisfy one or more** of the following criteria considered high risk for residual OSA after AT:

- Obesity (BMI > 95th percentile or z-score > 1.96 for age)
- Down syndrome
- African American race
- Pre-operative AHI > 10
- Age > 7 years
- Tonsils rated 1+ but persistent symptoms of OSA

Exclusion criteria: Patients with one or more of the following criteria will be excluded from the study:

- Craniofacial anomalies (including cleft lip and palate, Pierre Robin sequence)
- Genetic abnormalities
- Neuromuscular disorders (including cerebral palsy, hypotonia)
- Subglottic or tracheal stenosis
- Tracheostomy dependence

- Severe cardiopulmonary disease requiring supplemental oxygen at night
- Primary caregiver(s) are unable to complete questionnaires in English or Spanish, cannot be reached by telephone, or are planning to move during the study period

Recruitment: Daily clinic schedules will be reviewed by the PI or the research assistant to determine in advance which patients of participating providers might be eligible for the study based on the above inclusion and exclusion criteria. Two recruitment scenarios are anticipated: 1) Patients who have previously been diagnosed with OSAS by polysomnography and are referred to Pediatric Otolaryngology for consideration of AT: In this scenario the patients will proceed with surgery scheduling according to routine clinical care, with postoperative follow-up to be coordinated with the assistance of the RC to ensure timely follow-up and administration of follow-up questionnaires. 2) Patients referred to Pediatric Otolaryngology for consideration of AT for symptoms of sleep disordered breathing *without* a polysomnographic diagnosis of OSAS: These patients will be requested to undergo polysomnography prior to scheduling surgery in order to confirm the diagnosis of OSAS. Should any enrolled study subjects turn out to not have OSAS according to polysomnography, they will subsequently be excluded from the study and will be notified of such in writing.

Once the clinical decision is made by the pediatric otolaryngologist and family to proceed with AT, patients who meet the inclusion and exclusion criteria as noted above will be identified to the RC by the PI or collaborating pediatric otolaryngologist staffing the clinic. They will be informed of the study's purpose, risks, and benefits, and invited to participate. Parental written informed consent and child assent (if applicable) will be obtained by the research coordinator. The importance of the follow-up evaluation (questionnaires and postoperative sleep study) will be emphasized at enrollment. Also at that time, they will be provided with several questionnaires above and beyond the traditional clinical sleep questionnaires, including Infant/Toddler Quality of Life Questionnaire [ITQOL], which is a general quality of life instrument for patients 2 months through 5 years of age; Child Health Questionnaire [CHQ], a general quality of life instrument for patients 5 years through 18 years of age; a modified Epworth Sleepiness Scale [ESS], which measures daytime sleepiness in patients over the age of 5; and a neuro-cognitive instrument, called the Behavior Rating Inventory of Executive Function, or BRIEF. Each of these instruments has been in use for a number of years and has been well-validated through clinical and non-clinical studies, showing reliability and validity in a variety of settings and populations. Patients will have the option to complete these forms on paper or online. If they choose to complete the forms online, they will be allowed access to complete the questionnaires through OHSU's RedCap online database system; access will be restricted using a personalized password for each subject.

Consent and Assent: Written informed consent and authorization will be obtained from all parents or legal guardians of the patient participating in this study, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. The consent and authorization form includes information on the data repository as well as the primary study. If a parent's signature cannot be obtained, the investigator or RC will ensure that the

informed consent is signed by the patient's legal guardian. Only one parent's signature will be required (the study involves greater than minimal risk but includes the prospect of direct benefit to individual subjects). If the patient is a child between the ages of 7 and 18 and is cognitively able, assent from the patient will also be obtained. If the patient and/or the patient's legal guardian does not speak fluent English but does speak Spanish, they will be provided with a translated consent/assent form. Patients who do not speak English *or* Spanish will not be included in this study. Documentation of the consent process and a copy of the signed consent shall be maintained in the research record and patient's medical record.

Compensation and Costs: Patients' parents/guardians will be compensated for their study participation. They will receive $30.00 after completing the second set of questionnaires OR, if applicable, $75.00 after completing the second set of questionnaires and their child's post-surgery sleep study. They will not incur costs for the sleep endoscopy procedure (provided it takes place at the same time as their T&A). They may incur costs if their insurance applies cost-sharing to their polysomnography, but this procedure is medically important to managing patients at high risk for residual OSA and is considered part of routine clinical care.

Third party payers will incur costs related to the procedures in this study (sleep endoscopies and polysomnography), but, given the high risk nature of the patients who will be enrolled in this study, these procedures are reasonable, clinically indicated, and necessary in the proactive management of OSA and residual OSA.

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Termination and Withdrawal: Subjects have the right to withdraw from (i.e., discontinue participation in) this research at any time without any repercussions by notifying the principal investigator or the study coordinator either in writing or via email. If a subject decides to withdraw from this research study, the following research activities involving that subject's participation will be discontinued:

- Interacting or intervening with the subject in order to obtain data about him or her for the study (e.g., obtaining polysomnography or questionnaire data, initiating follow-up contacts with the subject) and
- Obtaining additional identifiable private information about the subject for the study by collecting or receiving additional information from any source (e.g., obtaining additional information from the patient's medical records)

Each patient may also withdraw from one component of the study (for example, the follow-up polysomnography), but may choose to allow the investigator to continue other research activities described in the IRB-approved protocol and informed consent document that involve participation of the subject, such as obtaining data about the patient through interaction with the patient (e.g., through follow-up interviews or physical exams). Also,

already-collected data about the patients will be retained and analyzed even if the patients choose to withdraw from the research.

The primary investigator may choose to terminate a patient's participation in the study for the following reasons: if polysomnography shows that the patient does not have OSA; if the investigator stops the study; and if the patient does not follow study instructions within a reasonable period of time (for example, if the patient is asked to complete post-surgery questionnaires, not having completed them twelve weeks later).

Sedation Protocol: Patients will be sedated with a combination of sevoflurane and dexmedetomidine similar to the protocols described in previous studies[46, 47]. In brief, patients will be premedicated with oral midazolam (0.5mg/kg) 20 minutes before induction of general anesthesia. General anesthesia will be induced using inhaled sevoflurane via face mask to allow insertion of an IV catheter. The sevoflurane will then be discontinued and sedation will be maintained with an infusion of dexmedetomidine (1 mcg/kg) with no loading dose and a bolus of ketamine (1 mg/kg) with the patient spontaneously breathing 100% O_2. This combination has been demonstrated to maintain general anesthesia while preserving respiratory drive and spontaneous breathing [44, 49]. Once sleep endoscopy has been completed, the dexmedetomidine infusion will be discontinued and anesthesia will be maintained using the standard sevoflurane-opiate-propofol combination that is typically administered for general anesthesia. The level of sedation will be continuously assessed using bispectral index monitoring to ensure an adequate sedation without causing oversedation.[48]

Sleep Endoscopy: Sleep endoscopy will be performed just prior to the adenotonsillectomy, under the same general anesthetic, thereby avoiding the need for a separate sedation. The endoscopy will be performed using either a 3.4mm or a 2.7mm flexible fiber optic endoscope (depending on age and size of the nasal passageway) which will be advanced trans nasally into the pharynx down to the level of the hypopharynx. We will take note of any obvious septal deviation or nasal obstruction as well as adenoid hypertrophy, and dynamic collapse at the level of the velum, oropharynx/lateral walls, tongue base, epiglottis, and supraglottis. The entire procedure should require no more than 10 minutes to complete. Relatively fixed structures such as the nasal airway and adenoids should require no more than approximately 1 minute to fully assess. The endoscope will then be held for approximately 2 minutes of observation above each subsequent site of potential dynamic airway collapse (the velum, oropharynx/lateral walls, tongue base, epiglottis/supraglottis). Should the airway obstruct in such a manner that the SpO_2 begins to decrease to a level below 85% for a continuous duration of at least 15 seconds, the endoscope will be removed and positive pressure ventilation via face mask will be used to restore the airway and re-oxygenate the patient. Once the SpO_2 has been returned to a normal level (>95%), endoscopy will resume, beginning from the previous point of cessation. Should the oxygen level decrease in a similar manner two more times, the endoscopy will be aborted entirely, and the patient will be intubated using an age-appropriate endotracheal tube in order to proceed with the adenotonsillectomy.

A total of 5 ENT surgeons in the group (including the Principal Investigator) will participate in patient recruitment and performance of DISE. Each endoscopic evaluation will be digitally recorded and a smaller subset will be later reviewed anonymously by two of the other four ENT surgeons who will not be familiar with the patient's history. These patients will have a total of 3 ratings at each anatomic site which will be averaged, and the average rating will be used in subsequent analysis. A subset of 30 patients will be rated a second time by the same raters one week later to determine intra-rater reliability. The validity of the findings on DISE is predicated on the idea that the proposed sedation protocol can achieve a level of sedation that reasonably mimics natural sleep. In order to ensure the proper level of sedation, we will plan to use a bispectral (BIS) index monitor which uses processed electroencephalographic signals to measure sedation on a unitless scale from 0 to 100 with 0 indicating coma and 100 indicating fully awake and conscious. Several studies have validated the use of the BIS monitor in children to reliably indicate the level of consciousness using a variety of anesthetic protocols.[68-70]

Airway Assessment: The subjective rating of the airway will be accomplished using a modified VOTE rating scale as originally described by Kezirian et al[49]. This rating scale allows assessment of the dynamic collapse of the airway characterized by location (Velum, Oropharynx/lateral walls, Tongue base, Epiglottis), pattern of collapse (anterior-posterior, concentric, lateral), and degree of obstruction (0-none, 1-partial, 2-complete). This rating scale has been demonstrated to have moderate to substantial interrater reliability with kappa values ranging from 0.4-0.8 depending on the specific structures being compared[50]. The kappa statistic is a quantitative measure of the magnitude of agreement between observers that is standardized to lie on a -1 to 1 scale where 1 is perfect agreement, 0 is what would be expected by chance, and -1 represents a perfect inverse relationship[51]. The typical interpretation of this statistic is presented in Table 1.

Table 1. Interpretation of Kappa Statistic

Kappa	Agreement
<0	Less than chance agreement
0.01-0.20	Slight agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Substantial agreement
0.81-0.99	Almost perfect agreement

Only four areas of the upper airway are included in the original VOTE classification as applied to adult airway assessments; we will break the rating down into the following areas: nasal airway (inferior turbinates, septum), nasopharynx/adenoids, velopharynx, oropharynx/tonsils, base of tongue/lingual tonsil hypertrophy/epiglottic retroflexion, and supraglottis. This is similar to the method described by Durr et al[52].

Surgery: Sleep endoscopy and adenotonsillectomy will be performed by one of five fellowship-trained pediatric otolaryngologists using standard techniques of tonsillectomy. Three commonly used methods will be employed which have all been well-described in the

literature as safe and effective techniques: 1) stainless steel (cold) instruments for both tonsillectomy and adenoidectomy and monopolar cautery for hemostasis, or 2) Monopolar cautery for both dissection of the tonsils during tonsillectomy and suction cautery for adenoidectomy, 3) microdebrider tonsillectomy and either of the previously described techniques for adenoidectomy.

Postoperative care: Although there is no broad consensus regarding the optimal protocol for post tonsillectomy monitoring, all patients <3 yrs of age or with severe OSA documented on a preoperative sleep study (AHI ≥ 10 or lowest oxygen saturation < 80%) will be admitted for overnight observation according to the Clinical Practice Guideline published by the American Academy of Otolaryngology-Head and Neck Surgery regarding the use of polysomnography prior to tonsillectomy in children[46]. Other patients will be monitored for at least an hour in the recovery room before being discharged, according to the usual postoperative protocol.

Follow-Up: Patients will either be seen in the otolaryngology clinic for a follow-up appointment or receive a post-surgery telephone or email contact by the study coordinator 1 to 2 months after their T&A. This clinic appointment or email or phone contact and the subsequent questionnaires the patients will be asked to complete (on paper or online) will allow assessment of relevant postoperative outcomes including standardized questionnaire responses and postoperative adverse events such as postoperative bleeding and/or dehydration. Patients will also be requested to return for a postoperative sleep study approximately 3 months after surgery (scheduled during the pre-operative period). Patients who are found to have residual sleep apnea during polysomnography will be asked to follow-up with a sleep medicine physician and the otolaryngologist who performed the adenotonsillectomy to consider further treatment options. These would include CPAP versus a repeat sleep endoscopy procedure to determine the pattern and location of residual obstruction. Adjunct surgery for residual OSA would be offered if indicated.

Assessment of Interrater Reliability: Although DISE and the VOTE classification have been demonstrated to have moderate to substantial inter-rater reliability in adults, we will confirm these findings in children; each endoscopic evaluation will be digitally recorded and later reviewed anonymously by two of the other four ENT surgeons who will not be familiar with the patient's history. Each patient will have a total of 3 ratings at each anatomic site which will be averaged and the average rating will be used in subsequent analysis. A subset of 30 patients will be rated a second time by the same raters one week later to determine intra-rater reliability. Inter-rater and intra-rater reliability for three independent raters will be calculated at each anatomic site using a kappa statistic with linear weighting.

Data Collection Procedures: Baseline and follow-up measures will be collected at initial clinic enrollment and 1 - 2 months postoperatively as summarized in Table 2. DISE will be performed at the time of AT. This 2 month interval should allow sufficient time to establish a new baseline with respect to OSAS and parental judgment of QOL while optimizing patient follow-up. At the time of subject enrollment, parents will be asked to schedule a follow-up sleep study 3 months after AT is scheduled. They will be reminded on the day of

surgery to schedule this post-operative sleep study and will be sent follow-up questionnaires with a self-addressed stamped envelope so that they can be returned by mail.

Table 2: Data Collection Variables/Schedule

Variable Type	Description		Baseline	1-3 Months
Polysomnography Components	Apnea-Hypopnea Index (AHI)		X	X
	Minimum Oxygen Saturation (Min SpO2)		X	X
	Desaturation > 3% Index		X	X
	Mean/Max End Tidal CO2 (ETCO2)		X	X
	% Total Sleep Time with ETCO2 > 45/50 mmHg		X	X
Generic Quality of Life (QOL)	Child Health Questionnaire (5-18 yrs) Infant/Toddler QOL Questionnaire (2mo-5 yrs)		X	X
Sleep-related QOL	OSA-18 Questionnaire Epworth Sleepiness Scale Pediatric Sleep Questionnaire (PSQ)		X	X
Executive Functioning	BRIEF Questionnaire		X	X
Physical Exam	Tonsil size Modified Mallampati/Friedman Tongue Position Body Mass Index (BMI)		X	
Sleep Endoscopy Rating Scale	Subjective ratings of degree of obstruction at 6 levels of the upper airway (described below)		X	
Potential confounders	<u>Demographic Variables</u> • Age, gender, race • Family composition • Family income, education • Smoke exposure	<u>Medical History Variables</u> • Down syndrome • Asthma • Environmental allergies • Nasal obstruction	X	X

Polysomnography: The gold standard for diagnosis of sleep apnea in children is overnight attended polysomnography which consists of cardiorespiratory recording including

oronasal airflow, oxyhemoglobin saturation, end-tidal carbon dioxide, electrocardiogram, pulse rate, pulse wave form, and calibrated respiratory inductive plethysmography (to assess respiratory effort) along with assessment of sleep staging by electroencephalogram, electrooculogram, and submental electromyogram.[53] Although a polysomnogram includes many output parameters, the primary parameter that is commonly used to diagnose and characterize the severity of OSA is the **apnea-hypopnea index (AHI)**. The definition of AHI often includes central (nonobstructive) events, but for the purposes of this proposal, AHI will be defined as the *number of obstructive apneas and hypopneas per hour of sleep*. An obstructive apneic episode is defined as cessation of oronasal airflow for two consecutive breathing cycles with continued respiratory effort while a hypopneic episode is a reduction of oronasal airflow of ≥30% for two consecutive breathing cycles with continued espiratory effort and associated cortical arousal or ≥3% oxyhemoglobin desaturation. Other commonly reported parameters are listed in Table 2.

Quality of Life Measures: Both generic and disease-specific quality of life (QOL) outcomes will be assessed as secondary outcomes in this study. Several studies have demonstrated poor QOL in children with OSAS especially in domains related to physical health outcomes,[54-56] and significant changes in QOL after treatment that have not always correlated with changes in polysomnographic parameters.[57] Lack of correlation between objective and subjective measures of disease has been demonstrated in many different disease processes including nasal obstruction and adult and pediatric OSAS.[58, 59]

Generic: **The Child Health Questionnaire (CHQ)[60]** and the **Infant Toddler Quality of Life Questionnaire (ITQOL)[61]** are validated generic quality of life instruments that are based on caregiver responses. The CHQPF28 is a 28-item short form questionnaire that assesses 14 physical and psychosocial concepts for patients ages 5-18 yrs. The ITQOL-47 is a 47 item questionnaire validated for infants and children aged 2 months to 5 years of age that assesses both child-specific concepts of overall health as well as parent-focused concepts related to caring for the child.

Sleep-related: The **OSA-18** is an 18 item validated questionnaire assessing five different domains of sleep-related quality of life, specifically sleep disturbance, physical symptoms, emotional distress, daytime function, and caregiver concerns.[62] This instrument has been used in many studies to demonstrate response to treatment after AT and has been shown to be valid and responsive to change.[63] The **Epworth Sleepiness Scale (ESS)** is a self-administered questionnaire with 8 questions. It provides a measure of a person's general level of daytime sleepiness, or their average sleep propensity in daily life, and is considered a standard worldwide.[77, 78] The **Pediatric Sleep Questionnaire (PSQ)** contains two validated scales: sleep-related breathing disorders like obstructive sleep apnea, and restless legs/periodic leg movements. The SRBD scale contains validated subscales for snoring, sleepiness, and daytime disruptive behavior.[79]

Executive Functioning: Executive functioning refers to skills that control and regulate other cognitive processes such as impulse control, mental flexibility, and working memory. The **Behavior Rating Inventory of Executive Function (BRIEF)** is a caregiver and

teacher-rated instrument assessing executive behaviors with three composite indices (Behavioral Regulation, Metacognition, and Global Executive Composite).[64] It was developed to assess the executive functions in children ages 5 to 18 years as observed by parents and teachers on a day-to-day basis and has commonly been used in studies assessing symptoms of attention deficit/hyperactivity disorder (ADHD). The original 86-item Parent Form was shortened to a 24-item abbreviated version with similar psychometric properties as the original scale.[65] The BRIEF-P is a version that was adapted for use in pre-school age children aged 25-74 months with similar psychometric properties.[69]

VII. Analysis

Statistical Power and Sample Size: Based on the preliminary data described in section 3.C.2, we estimate that approximately 200 patients per year will be eligible for study inclusion. If we assume a 50% enrollment, this equates to 450 patients over the first 4.5 years of the award period. We will aim for 80% patient retention; however we recognize the possibility of a lower rate of follow up. If we assume 50% attrition, this results in 225 patients who will complete the study protocol. To simplify the power calculation, we chose to treat the SERS findings as a simple sum of the scores of the six anatomic sites (SERS Total Score). In the final analysis, depending on the results of Aims 1 and 2, we may choose to use a subset or a weighted linear combination of the scores at the individual anatomic sites.

Aim 1: Preliminary data is available from the retrospective review of patients who previously underwent DISE at the time of AT and have preoperative sleep study data available (n = 20). Using this data, we estimate that the mean correlation between the SERS Total Score and OAHI is rho = 0.4 (Pearson correlation coefficient). If we assume a null hypothesis of rho = 0.2 (weak correlation), using a Fisher's Z-r transformation with a sample size of 225, we should have >90% power to detect this difference. This sample size assumes 50% attrition, but because these calculations are all based on baseline measures, the true sample size for Aim1 should be 450, thus we should have excess statistical power for further adjusted and subgroup analysis.
Aim 2: We modeled the SERS Total Score as a predictor in a logistic regression model with presence of post-AT OSA as a binary outcome variable, using OAHI > 5 as a cut-off for diagnosis (a conservative threshold). From this calculation we obtained a beta0 constant = -3.58 and beta1 coefficient = 0.764, with a mean and standard deviation for the SERS Total Score for three surgeons = 5.59 (SD 2.07). Assuming a normal distribution of the data, we would need only 32 patients to have at least 90% power to detect a significant association between the SERS Total Score and the outcome of interest. Since we anticipate a sample size of 225, this should be more than sufficient to accomplish Aim 2 and provide sufficient power for subgroup analyses and further adjusted analysis.
Aim 3: We plan to divide the cohort evenly between a training set and a validation set so that each set would include 112 patients. A similar regression model was constructed as in Aim 2 except we also included several additional covariates including BMI z-score, tonsil size, and lowest oxygen saturation. With this limited model, with a sample size of 112, we

calculate >90% power to detect a significant association with the primary outcome of presence of post-AT OSAS.

Data Analysis:

Analyses

Aim 1: The objective of this aim is to evaluate the reliability of the proposed SERS and to test its correlation with several baseline measures of OSAS disease burden: 1) OSAS severity on polysomnography, 2) QOL measures, both generic and OSAS-specific, and 3) executive functioning. Our hypothesis is that *complete obstruction at any level* observed during DISE will be associated with *greater severity of OSAS* with respect to objective and subjective outcomes compared to patients with partial obstruction (Hypothesis 1).

Reliability: Inter-rater and intra-rater reliability for three independent raters will be calculated at each anatomic site using a kappa statistic with linear weighting. Previous studies investigating the reliability of similar rating scales have reported kappa scores of DISE ratings in the range of 0.4-0.8.[40, 71] Our preliminary data suggest comparable reliability of the proposed SERS, but in order to confirm the reliability in this cohort, we will plan on performing a preliminary analysis based on the first 30 patients enrolled. If the minimum kappa range does not exceed 0.5, we will conduct an additional group training session to arrive at more precise definitions of the different anatomic levels and the degree of obstruction at each level. These refined ratings will then be applied to the videos for the subsequent 30 subjects enrolled to confirm adequate reliability.

Correlation of DISE with Baseline Sleep Apnea Severity: Spearman correlation coefficients will be calculated for the mean obstruction at each anatomic site against the baseline AHI and the secondary outcomes listed in Table 3. Subgroup analysis will be conducted for each of the high-risk subgroups. Compared to patients with only partial obstruction, we expect to demonstrate strong correlation between complete obstruction at any level and 1) increased severity of OSAS, 2) worse quality of life, and 3) worse executive functioning. Moreover we expect that greater sites of complete obstruction will correlate with worse disease burden. Exploratory analysis of independent correlations between each anatomic site and OSAS outcomes may suggest that certain anatomic sites have stronger correlations with disease severity than others.

Dependent (Outcome) Variable	**Independent (Explanatory & Adjustment) Variables**	**Statistical Method**	**Test For:**
PRELIMINARY BIVARIATE ANALYSES			
AHI (continuous)	Complete obstruction at any site (dichotomous)	T-test, Mann-Whitney*	Unadjusted correlation

AHI (continuous)	Sleep Endoscopy Rating at each anatomic site (ordinal)	Spearman correlation coefficient	Correlation
AHI (continuous)	Each Potential confounder	T-test, Mann-Whitney* Spearman correlation	Find sig confounders to adjust
PRIMARY ANALYSIS (PRIMARY HYPOTHESIS*)*			
AHI (continuous)	• Complete obstruction at any site (dichotomous) • Sig confounders	MV linear regression	Independent association
SECONDARY ANALYSES (SECONDARY HYPOTHESES)			
• AHI (continuous) • Other polysomnography measures (continuous) • CHQ/ITQOL (continuous) • OSA-18 (continuous) • BRIEF score (continuous)	• Complete obstruction at any site (dichotomous) • # sites with complete obstruction (ordinal) • Sleep Endoscopy Rating at each anatomic site (ordinal) • Sig confounders	MV linear regression	Independent association
RELIABILITY ANALYSIS			
• Sleep Endoscopy Rating (ordinal)	• Sleep Endoscopy Rating (ordinal)	Kappa statistic	Inter-rater reliability Intra-rater reliability

Table 3: Aim 1 Analyses

*MV = Multivariable. * Non-parametric testing if outcome variables not normally distributed*

Aim 2: The objective here is to determine the relationships between the degree and pattern of obstruction observed on baseline DISE and the outcomes after AT, using the same measures as those in Aim 1.

DISE Associations with Outcomes of AT: Analyses for Aim 2 will be similar to those performed in Aim 1, except the primary outcome of interest will be presence of residual OSAS by polysomnography after AT. We will use a dichotomous outcome with a conservative threshold for diagnosis of AHI > 5. Though higher than the typical threshold of AHI > 1 for diagnosis of OSAS in children, this is a more clinically meaningful threshold suggesting at least a moderate degree of residual OSAS. Secondary outcomes will include the severity of post-AT OSAS and the magnitude of change from baseline. To account for the different contributions of each anatomic site to the overall level of obstruction, factor analysis will be performed to determine the optimal weighting of each anatomic site. The association between this composite rating scale variable and the outcomes of interest will then be tested using multivariable regression analysis (Table 4). Our hypothesis is that patients with obstruction at sites other than the tonsils or adenoids will have greater risk of residual OSAS and decreased improvement from baseline in all outcome measures. In addition,

we expect to identify specific sites where obstruction is most strongly associated with AT failure. We will perform subgroup analyses to assess for these relationships within high-risk subgroups.

Table 4. Aim 2 Analyses

Dependent (Outcome) Variable	**Independent (Explanatory & Adjustment) Variables**	**Statistical Method**	**Test For:**
PRELIMINARY BIVARIATE ANALYSES			
Postop AHI (continuous)	Total obstruction at non-T&A site (dichotomous)	T-test, Mann-Whitney*	Unadjusted association
Postop AHI (continuous)	DISE Rating at each anatomic site (ordinal)	Linear regression, Spearman correlation	Unadjusted association
Postop AHI (continuous)	Each Potential confounder	T-test, Mann-Whitney*	Find sig confounders to adjust
PRIMARY ANALYSIS (PRIMARY HYPOTHESIS*)*			
• Residual OSA (dichotomous)	• Total obstruction at non-T&A site (dichotomous) • Sig confounders	• MV logistic regression	Independent association
SECONDARY ANALYSES (SECONDARY HYPOTHESES)			
• Δ AHI (continuous) • Δ CHQ/ITQOL (continuous) • Δ OSA-18 (continuous) • Δ BRIEF score (continuous)	• Total at non-T&A site (dichotomous) • # sites with complete obstruction (ordinal) • DISE Rating at each anatomic site (ordinal) • Sig confounders	• MV logistic regression • Factor analysis	• Independent association • Optimize weighting of site ratings

*MV = Multivariable. * Non-parametric testing if outcome variables not normally distributed*

Aim 3: Our goal here is to develop a comprehensive model that includes pre-AT DISE ratings, demographic variables, physical exam findings, baseline OSAS severity, and relevant comorbidities to predict the outcomes of AT. We will then validate this model in an independent sample of patients. During model development, the statistical analysis used to identify relevant component variables and associated weighting factors will involve two strategies: 1) multivariate regression analysis, and 2) conjunctive consolidation.[72-74] Baseline variables will be tested for unadjusted associations with AT outcomes (Table 5). Significant independent variables ($p<0.20$) will be included in the final regression model, and weights will be proportional to the strength of association with post-AT AHI. The final multivariate models will be constructed in a stepwise manner with a significance level for entry of 0.05 and for removal 0.10.

A second sleep endoscopy staging system will be developed using conjunctive consolidation. Significant ($p<0.20$) variables from simple bivariate associations with

AT outcomes will be used to build the final model. The relevant variables will be merged in a series of steps using the principles of conjunctive consolidation.[72-74]

Table 5. Variables for Predictive Model of AT Outcomes

	Variables	Variable Type	Instrument development	Instrument Validation
Sample (N)			112	112
Predictor (Independent) Variables	DISE Rating Scale *	Ordinal	X	
	Baseline AHI, QOL	Continuous	X	
	BMI Z-score	Continuous	X	
	Age at Surgery	Continuous	X	
	Comorbidity	Categorical	X	
	Demographics	Categorical	X	
Primary Outcome (Dependent) Variable	Post AT OSA	Binary	X	X
Secondary (Dependent) Outcome Variables	Δ AHI	Continuous		X
	Δ OSA-18	Continuous		X
	Δ BRIEF score	Continuous		X
	Δ CHQ/ITQOL	Continuous		X

**Total score, specific anatomic site ratings, or combination of linear weights per analysis in Aim 2*

VIII. Study Duration

Timeline: As noted in the preliminary studies section above, we anticipate at least 200 patients per year will meet inclusion/exclusion criteria. This is likely a conservative estimate, as it is based on aggregate surgical volume when two of the participating surgeons were new to the department and not yet fully active. If we estimate that only 50% of eligible subjects agree to participate, then we can anticipate approximately 100 patients enrolled per year for a total of 450 patients after 54 months. With a minimum follow-up of 3 months, data collection should be completed after 57 months (Table 6).

Table 6: Anticipated Timeline

	Year 1		Year 2		Year 3		Year 4		Year 5	
Coursework										
Data Collection										
Analysis Aims 1 & 2										
Analysis Aim 3										
Manuscript										
Prepare R01										

IX. Changes to Protocol

Any modification of this protocol will be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the OHSU IRB, before the revision or amendment is implemented.

X. Data Protection

Baseline data will be collected at the time of study enrollment by a research coordinator (RC) who will also obtain informed consent for study participation. Follow-up questionnaire data will be collected at the one to two month follow-up visit, by mail, or online through a secure REDCap website if parents have internet access. Only the PI and members of the study team will have direct access to identifiable private information. All data extracted from the Electronic Medical Record (EMR) or paper questionnaires will be input by either the PI or RC into a password-protected REDCap database stored on firewall-protected institutional servers maintained by the Oregon Clinical and Translational Research Institute (OCTRI). Subjects will be assigned a unique randomly generated study identification number and extracted datasets will be coded for use in subsequent analysis. Paper copies of questionnaires will be stored in a locked file cabinet in the PI's office and only the PI or RC will have direct access to these files. Videos of sleep endoscopy examinations will be uploaded to an institutional firewalled password-protected server at the time of video capture by the PI or his clinical collaborators. These videos will then be copied, edited, and coded for subsequent rating and analysis. Edited videos will be stored in a separate research file on the institutional server. No published materials will reveal the identities of any patient participating in the study. The database will be maintained until all pertinent research is concluded or one year after collection of follow-up data for the last subject enrolled, whichever occurs first. At that time, all paper records will be shredded and all computer database files will be deleted, other than the IRB-approved repository.

Data Management and Quality Control: To ensure consistency and reliability of DISE assessments, all participating ENT surgeons will undergo a detailed training session to review both the sedation protocol and the SERS. In addition, the PI will observe patient enrollment, data collection, and DISE assessments for each collaborating surgeon every 3 months to ensure consistency in research procedures.

XI. Data Safety Monitoring

Data and safety monitoring will be the responsibility of the principal investigator. The following is an outline of the roles and responsibilities of the study PI and the research coordinator. All study staff will be trained on the protocol and the data and safety monitoring plan. The following activities and responsibilities for data and safety monitoring for the proposed study are the following:

1) **Principal Investigator:** The PI will be responsible for all aspects of data and safety monitoring including but not limited to: assuring written informed consent is obtained from a parent and assent from the child (when appropriate); verifying inclusion/exclusion criteria for all subjects prior to surgery. PI will review dropouts, adverse events and protocol deviations in real time, to determine if the events require medical follow-up and/or IRB reporting. Comprehensive adverse event (AE) and protocol deviation (PD) reports will be reviewed for trends quarterly. If AE or PD trends are identified the PI will determine appropriate course of action (e.g. protocol revision, staff retraining, IRB notifications, etc.). The PI will review enrollment monthly until the study recruitment is met.

2) **Research Coordinator:** A research coordinator will record AEs from the medical records, and solicit self-reporting of adverse events from the subjects after surgery, and again at the one to two month follow up. The research coordinator will report AEs and PDs to the PI within one working day of becoming aware of an event, and compile a list of all AEs for the PI in preparation for IRB continuing review. The research coordinator will provide the PI an enrollment report on a monthly basis until enrollment is met.
3) **OHSU Institutional Review Board:** Fatal and life-threatening UPs will be reported to OHSU IRB and the NHLBI within 7 days of notification of the event. All other UP reports will be submitted to OHSU IRB and the NHLBI no later than 15 days after occurrence or notification of the event.
4) **Data integrity and security:** Computers at the site connected to the internet will be used to collect data that is directly entered into the REDCap database. REDCap employs a variety of data verification features including limiting entries by data type, using drop-down menu items, and setting range limits. Further data confirmation by the RC will occur by visual verification at time of data entry. The REDCap electronic database is stored behind the OHSU firewall. It will be password-protected and only PI and IRB approved study staff will have access to any study data. Each patient will have a unique patient ID number; patient names will not be included in REDCap database reports or subsequent data analysis.

XII. Potential Benefits of the Proposed Research to Human Subjects and Others

Potential direct benefits*:* Patients may potentially benefit directly from this study by three mechanisms:

1) **Confirmation of OSAS diagnosis and severity by polysomnography:** It is possible that patients who have not previously been tested and are referred for pre-AT polysomnography may be found to have a normal study. This would rule out clinically significant OSAS in which case AT would be unnecessary, so the patient would be saved the risks and discomfort of undergoing a surgical procedure. In this scenario, the patient would then be excluded from further study. Conversely, if the patient is found to have severe OSAS, this could alter the perioperative management so that a patient who might otherwise be treated as an outpatient would be admitted for overnight observation. If the OSAS is severe enough, admission to the intensive care unit postoperatively might be indicated for more vigilant monitoring and prevention of perioperative complications.
2) **Characterization of nature of obstruction by sleep endoscopy**: If the sleep endoscopy reveals an unexpected finding with respect to location or pattern of airway obstruction such as collapse at the base of tongue or supraglottis, this finding might suggest strategies for further intervention in the event that the patient is diagnosed with residual OSAS after AT.
3) **Confirmation of cure or presence of residual OSAS based on postoperative polysomnography**: Most patients undergoing AT for OSAS are inconsistently followed postoperatively despite the high rate of residual disease in this population of patients. Thus patients with significant residual OSAS may be left untreated with the potential for long term sequelae of incompletely treated OSAS. Because all patients in this study will be asked

to follow-up for postoperative polysomnography, patients with residual OSAS will be identified and the need for further follow-up or intervention will be clearly indicated.

Potential benefit to future patients: Development of a predictive model of AT outcomes can potentially benefit future patients by allowing accurate and reliable prognostication of AT outcome based on anatomic predictors of surgical success. This could help to identify patients who are likely to fail AT alone and possibly suggest the need for alternative treatments including non-surgical treatment (e.g. oral appliances) or adjunct procedures that could be implemented *at the time of the initial surgery* which could decrease the prevalence or severity of residual OSAS as well as save the patient the risk of a second surgical procedure and general anesthetic.

Importance of the knowledge to be gained: The knowledge gained from this project will allow more accurate prognostication of the outcome of AT and thus facilitate more individualized treatment plans based on individual patient risk factors. In addition, the findings of this study may give greater insight into the mechanism of failure of AT and suggest more effective therapeutic interventions for those patients who are likely to fail AT. This study has the potential to allow improvement in individual surgical outcomes and could lead to more cost-effective delivery of health care through more efficient targeting of patients who are most likely to benefit from AT, thus decreasing the need for secondary interventions whether surgical or non-surgical and thereby decreasing health care utilization among children with OSAS.

XIII. Potential Risks

The subjects in this study are scheduled to have a tonsillectomy or adenotonsillectomy. That procedure is not experimental and is not part of this study.

One risk to taking part in this study is that the sleep endoscopy subjects receive may not be effective in treating OSA. The study may not provide subjects with any actual health-related benefits. The risks of sleep endoscopy itself are minor. Previous studies have demonstrated that drug-induced sleep endoscopy can be done safely in adults and children with no adverse events reported either during or immediately after sleep endoscopy. Subject vital signs will be carefully monitored as is the standard protocol during any operative procedure. These include heart rate, blood pressure, oxygen saturation, and end tidal CO_2 levels. The primary risk is an apneic event due to either airway obstruction or over sedation. Because the goal of the endoscopy involves visualizing the dynamic collapse of the airway during respiration in as natural a state as possible, this requires that the subject is kept breathing spontaneously without an endotracheal tube or other airway intervention in place to maintain a stable airway. **If an obstructive event resulting in oxygen desaturation or cardiopulmonary instability were to occur, the appropriate personnel and equipment required to secure a stable airway (i.e. the Anesthesiology team and the Otolaryngology team) will already be present.** Repeated airway obstruction resulting in prolonged oxygen desaturation below 90% will result in aborting of the endoscopy procedure and intubation of the patient for the remainder of the procedure. The duration of the endoscopy would also necessarily extend the operative

time, but typically the duration of endoscopy lasts no longer than 5-10 minutes. Since this represents a relatively small proportion of the overall operating time (typically 25-30 minutes), this poses little additional risk to the subject with respect to duration of general anesthesia.

The endoscopy may give subjects a sore throat. However, the T&A will make a subject's throat sorer than the endoscopy by itself. Appropriate pain medication will be prescribed. There is a small chance a subject's esophagus may bleed or the subject may get an infection. Rarely, an endoscopy makes a hole in someone's esophagus. This happens about 1 time in every 5,000 endoscopies. If this happens to a subject, they may need additional surgery to repair the hole.

Sleep studies are very low risk events. Obtaining sleep studies may be inconvenient for subjects and families. The sleep study location may not be near their home, and they may need to find alternate care for other family members overnight. The wires and monitors worn during the sleep study may be uncomfortable or frightening. Subjects may not get a full night of quality sleep while undergoing a sleep study.

Subjects in the study will complete several questionnaires (instruments). All of these questionnaires have been in use for many years and have been tested and proven to provide valuable information and assessment. Although the majority of questions on these forms concern general health and sleep habits, some of these questions may seem personal or embarrassing and may upset the subject. Subjects may refuse to answer any of the questions that they do not wish to answer. If the questions make them very upset, we will help them to find a counselor.

Certain risks may result from storage of information in a repository and/or use of information in future research studies. Despite our best efforts to protect patients' identities, breaches of confidentiality could occur. Such a breach could cause mild psychological trauma or a loss of confidence in OHSU. Breach of confidentiality could impact insurability, employability, family plans, and family relationships, although the risks of this are low as we will not be recording mental health or family status information for this study. There could also be a risk of stigmatization for the subject if details of certain medical disorders are made known publically.

Other Potential Problems and Alternative Approaches:

- *Similarity between DISE and Natural Sleep*: Several studies investigating adult DISE have concluded that propofol-induced sedation is a reasonable mimic of natural sleep because it does not induce symptoms of OSAS in control subjects without a diagnosis of OSAS or are non-snorers, whereas snoring and obstruction were observed among patients with a history of OSAS.[75, 76] Among children, both propofol and dexmedetodomine have been utilized as sedating agents, and both have been observed to induce sedation that produces snoring and obstruction while preserving spontaneous breathing. Regardless of the agent used, drug-induced sedation is likely to be a closer mimic of natural sleep than awake examination, and

we will use the BIS monitor as previously described to help ensure an adequate and consistent level of sedation. Should the findings in Aims 1 and 2 suggest inadequate reliability of the sedation protocol, we will consider the use of propofol as a primary sedating agent as in reports of adult DISE.

- *Lack of Association Between SERS and baseline OSAS severity (Aim 1) or outcomes of AT (Aim 2)*: Though previous studies and our preliminary data suggest an association between significant obstruction observed on DISE and both the severity of disease at baseline and the response to AT, it is possible that no significant associations will be observed (null hypothesis in Aims 1 and 2). However, as part of Aim 2, we will plan on an exploratory analysis including factor analysis to determine if the different components of the SERS can be weighted or combined to optimize the strength of association with the outcomes of interest. This optimized variable will be applied only in the training set for development of the predictive model in Aim 3. Testing of the model in an independent sample of patients will ensure its validity. In this setting, it is still possible that individual items or some combination of the SERS could be included with other potential risk factors (demographics, comorbidities, physical exam findings) to generate a model that is predictive of AT outcome. However, it is possible that the most predictive model may not ultimately include any DISE findings. Such a model would still be a useful clinical tool and is in fact similar to predictive models that have previously been proposed. Thus, even a negative result in Aims 1 and 2 would not preclude a useful result of Aim 3.
- *Low Enrollment and Patient Retention*: To anticipate possible low enrollment, we have planned for only 50% enrollment among eligible subjects. Because the primary procedures in this study are clinically indicated, it is likely that enrollment will be higher than this. We will review enrollment data every 6 months and if it is slower than expected we will consider loosening inclusion criteria such as including overweight in addition to obese children. With respect to patient retention, because there is typically significant symptomatic improvement with AT, parents are less inclined to follow-up routinely unless their child remains significantly symptomatic. For these reasons, we are prepared for a 50% attrition rate among enrolled subjects. The importance of postoperative follow-up will be emphasized to parents at study enrollment. Parents will also receive voice and email reminders (if available) to return questionnaires and follow-up for postoperative sleep studies. Finally, a $50 remuneration at the completion of data collection will provide additional incentive to complete the study protocol. Analysis will be performed to determine if patients lost to follow-up differ significantly in baseline characteristics from subjects who complete the study protocol.

Future Directions: With a model that can accurately predict the outcome of AT, we can then propose a trial, possibly randomized, of standard treatment for pediatric OSAS (AT) compared to DISE directed surgery to determine if improved outcomes can be achieved with an alternative surgical intervention. In addition, we are planning a follow-up study that includes repeating DISE in patients with sufficient post-AT OSAS to warrant further surgical intervention. Findings of the post AT DISE could then be compared to the initial endoscopy findings to see if the dynamics of airway obstruction changed significantly after

AT. Further studies would include refining the predictive model and applying it in all AT patients to determine if it could be generalized beyond the high-risk groups specified in this proposal.

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