Title:	**Cerebral blood flow and neurocognition in children with obstructive sleep apnea**
Short Title	CBF and childhood OSAS
Sponsor:	National Institutes of Health
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ABBREVIATIONS AND DEFINITIONS OF TERMS

AHI	Obstructive apnea hypopnea index
CBF	Cerebral blood flow
DOS	Diffuse optical spectroscopy
DCS	Diffuse correlation spectroscopy
$ETCO_2$	End-tidal CO_2
NBT	Neurobehavioral testing
NIRS	Near-infrared spectroscopy
OSAS	Obstructive sleep apnea syndrome
SpO_2	Oxyhemoglobin saturation
StO_2	Tissue oxygen saturation
THC	Total hemoglobin concentration
$TcCO_2$	Transcutaneous CO_2

ABSTRACT

Context:

- Children with the obstructive sleep apnea syndrome (OSAS) have impaired behavior and cognition compared to normal controls.
- OSAS is characterized by repetitive occlusion of the upper airway during sleep that results in hypoxemia, hypercapnia and arousal from sleep.
- Previous studies in adults with OSAS have shown significant alterations of cerebral blood flow during wakefulness and sleep and our preliminary data showed blunted cerebral blood flow response to hypercapnia in children with OSAS during wakefulness. However, it is unknown whether children with OSAS also have impaired cerebral blood flow during sleep.
- It is unknown whether the deficits in behavior and cognition in children are associated with cerebral blood flow dysregulation.
- We hypothesize that children with OSAS have an impaired cerebral blood flow during wakefulness and sleep as compared to normal controls. We further hypothesize that the degree of this impairment will correlate with neurocognitive function.

Objectives:

- To investigate whether the changes in cerebral blood flow during wakefulness and sleep elicited by hypercapneic challenge, differ in children with OSAS compared to normal controls.
- To investigate the changes in cerebral blood flow during wakefulness and sleep elicited by hypercapneic challenge in children with OSAS before and after treatment (adenotonsillectomy, adenoidectomy, or tonsillectomy).
- To investigate whether the changes in cerebral blood flow elicited by the aforementioned testing correlate with neurocognitive outcomes.

Study Design: Case-control study

Setting/Participants:

- Children's Hospital of Philadelphia, Pulmonary Division, outpatient offices
- Children with OSAS aged 6-12 years will be recruited following a clinical polysomnogram. Normal age- and gender-matched controls will be recruited from the general community.

Study Interventions and Measures:

- The following procedures will be performed in OSAS subjects pre- and post-adenotonsillectomy, and controls:

- Sleep study at baseline, 6 and 12 months. For OSAS participants, there will be an additional sleep study 6-12 week post clinically indicated surgical treatment to assess resolution of OSAS.

- Neurocognitive testing at baseline, 6 and 12 months for controls

- Neurocognitive testing at baseline, and 6 and 12 months after clinically indicated surgical treatment of OSAS for children with OSAS

- Measurement of cerebral blood flow by NIRS during wakefulness and sleep during hypercapneic challenge at baseline, 6 and 12 months for controls

- Measurement of cerebral blood flow by NIRS during wakefulness and sleep during hypercapneic challenge at baseline, 6 and 12 months after clinically indicated surgical treatment of OSAS for children with OSAS

- Monthly telephone calls for retention purposes and assessment of adverse events.

PROTOCOL SYNOPSIS

Study Title	Cerebral blood flow and neurocognition in children with obstructive sleep apnea
Funder	National Heart, Lung, and Blood Institute (NHLBI)
Study Rationale	The rationale of this case-control study is to identify the mechanisms of neurocognitive dysfunction in children with the obstructive sleep apnea syndrome (OSAS). OSAS is common. It occurs in 2-3% of children and if left untreated, is associated with important complications such as hypertension, endothelial dysfunction, and cognitive and behavioral impairment. This is important as children's brains are developing and thus, the long-term consequences of cognitive and behavioral dysfunction may have great impact on their adult life. Imaging studies of adults with OSAS have identified abnormal morphology of the frontal cortex, an important area for executive function. Other studies using magnetic resonance spectroscopy imaging (MRSI) have shown altered central nervous system metabolites of neuronal white and gray matter in adult and children with OSAS, which may be indicative of neuronal injury. Researchers have hypothesized that this neuronal injury results in cognitive and behavioral consequences, and is caused by OSAS-associated hypoxemia. OSAS, however, is not only characterized by periods of hypoxemia. OSAS patients experience hypercapnia and frequent arousals from sleep as well, as a consequence of the repetitive episodes of upper airway obstruction that are the hallmark of OSAS. This study will further identify the mechanisms of behavioral and cognitive dysfunction in children with OSAS by measuring cerebral blood flow changes in children with OSAS, and controls during hypercapneic challenges during wakefulness and correlating these results with measures of cognition and behavior. In addition, all participants will be retested over 1 year approximately to evaluate changes in behavior, cognition and cerebral blood flow related to treatment of OSAS vs. development.
Study Objective(s)	**Primary** • To determine the changes in cerebral blood flow in children with OSAS and controls measured by near-infrared spectroscopy during wakefulness and sleep, elicited by hypercapneic challenge. **Secondary** • To determine the correlation between changes in cerebral blood flow in children with OSAS and controls measured by the aforementioned testing, and cognitive and behavioral measures

	• To determine the changes in cerebral blood flow in children with OSAS, measured by near-infrared spectroscopy during wakefulness and sleep, elicited by hypercapneic challenge after clinically indicated surgical treatment of OSAS. • To determine longitudinal changes in cerebral blood flow in controls, measured by near-infrared spectroscopy during wakefulness and sleep, elicited by hypercapneic challenge over one year. • To determine the correlation between changes in cerebral blood flow in children with OSAS after treatment of OSAS measured by the aforementioned testing, and cognitive and behavioral measures.
Study Design	Case-control study
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria (OSAS Subjects)** 1. Subjects age 6-12 years 2. Absence of neurologic, cardiovascular, pulmonary or any other chronic illness. 3. No prior surgery on the nose, palate or oropharynx 4. No current drug intake that may interfere with testing such as sedatives or stimulants 5. No prior treatment of sleep-disordered breathing. 6. Polysomnographic recording criteria: subjects with OSAS must have an obstructive apnea hypopnea index (AHI) ≥ 5/hour. 7. Parent/guardian permission (informed consent) and if appropriate, child assent. **Exclusion Criteria (OSAS Subjects)** 1. Previous adenotonsillectomy 2. Previous use of CPAP 3. Craniofacial anomalies 4. Genetic syndromes (e.g. Trisomy 21, Prader-Willi) 5. ADHD on medication 6. Developmental delay as determined by receiving a score <70 on the ABAS-III 7. Non-English speakers due to the nature of neurocognitive testing **Inclusion Criteria** (Control Subjects) 1. Subjects age 6-12 years

	2. Absence of neurologic, cardiovascular, pulmonary or any other chronic illness. 3. No prior surgery on the nose, palate or oropharynx 4. No current drug intake that may interfere with testing such as sedatives or stimulants 5. No prior treatment of sleep-disordered breathing. 6. Polysomnographic recording criteria: normal control subjects must have an AHI ≤1.5/hour. 7. Parent/guardian permission (informed consent) and if appropriate, child assent. **Exclusion Criteria (Control Subjects)** 1. Previous adenotonsillectomy 2. Previous use of CPAP 3. Craniofacial anomalies 4. Genetic syndromes (e.g. Trisomy 21, Prader-Willi) 5. ADHD on medication 6. Developmental delay as determined by receiving a score <70 on the ABAS-III 7. Positive Pediatric Sleep Questionnaire. 8. Non-English speakers due to the nature of neurocognitive testing
Number Of Subjects	70 controls, 70 subjects with OSAS. Single site: CHOP.
Study Duration	Each subject's participation will last 12-14 months approximately.
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: screening for eligibility and obtaining consent (2) Observation Period: measurements made for monitoring control and OSAS participants over time.
Efficacy Evaluations	Changes in cerebral blood flow
Safety Evaluations	Vital signs will be monitored throughout testing.
Statistical And Analytic Plan	A sample size of 50 in each group (total N = 100) will have 80% power to detect a moderate CBF changes effect size of 0.566 using a two group t-test with a 0.05 two-sided significance level. We plan to recruit 70 in each group to account for attrition.
DATA AND SAFETY MONITORING PLAN	Independent medical monitor and DSMB (both mandated by NHLBI)

TABLE 1: SCHEDULE OF STUDY PROCEDURES PARTICIPANTS WITH OSAS

Study Phase	**Screening+**									
Visit Number	**Screening+**	**1**	**2**	**3**	**Phone***	**4**	**5**	**Phone***	**6**	**7**
Notes		**Night**	**Day**	**Post-op**	**Monthly ***	**Day**	**Night**	**Monthly ***	**Day**	**Night**
Informed Consent/Assent	X									
ABAS-III	X									
Review Inclusion/Exclusion Criteria	X									
Demographics/Medical History	X									
Mallampati/ tonsillar size assessment	X		X							
Height and Weight	X	X		X			X			X
Sleep study	X (if not done clinically)			X						
Sleep Study with CBF Measurements	X (if clinical sleep study already done)	X (if necessary)					X			X
CBF Daytime Measurements			X			X			X	
Cognitive and behavioral testing			X			X			X	
Adverse Event Assessment		X	X	X	X	X	X	X	X	X

+If the Screening visit is not needed (i.e., participant has already had a clinical sleep study), the Screening Visit and Visit One will be combined into Visit 1.

*In order to assess for AEs as well as for retention purposes, each participant will receive a monthly telephone call during the months that a visit to CHOP is not required.

TABLE 2: SCHEDULE OF STUDY PROCEDURES CONTROL PARTICIPANTS

Study Phase	**Screening**	**Observation Study Visits**							
Visit Number	**1**	**2**	**3**	**Phone***	**4**	**5**	**Phone***	**6**	**7**
Notes		**Day**	**Night**	**Monthly***	**Day**	**Night**	**Monthly***	**Day**	**Night**
Informed Consent/Assent	X								
ABAS – III	X								
Review Inclusion/Exclusion Criteria	X								
Demographics/Medical History	X								
Mallampati/ tonsillar size assessment		X							
Height and Weight	X		X			X			X
Sleep study	X								
Sleep Study with CBF Measurements			X			X			X
CBF Daytime Measurements		X			X			X	
Cognitive and behavioral testing		X			X			X	
Adverse Event Assessment		X	X	X	X	X	X	X	X

*In order to assess for AEs as well as for retention purposes, each participant will receive a monthly telephone call during the months that a visit to CHOP is not required.

FIGURE 1: GENERAL STUDY DIAGRAM

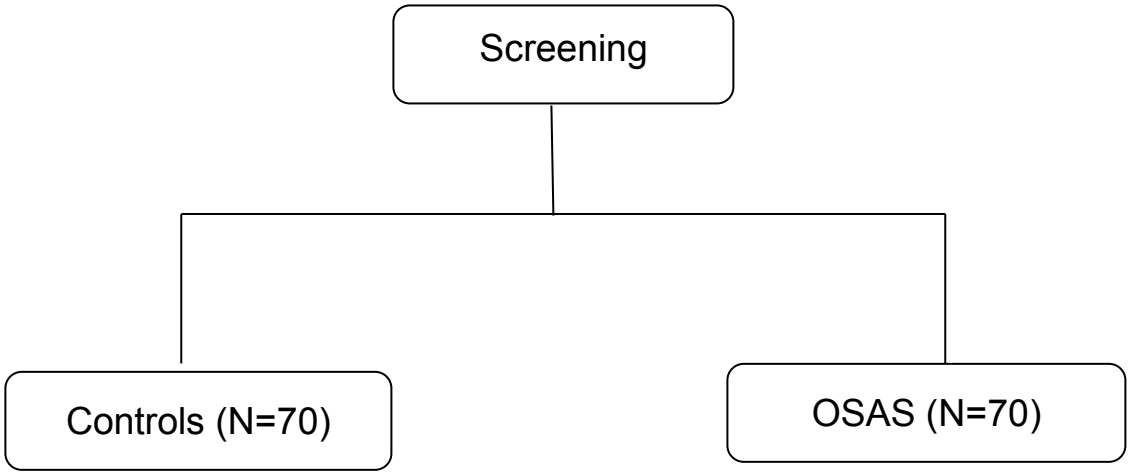


FIGURE 2: OSAS STUDY VISIT DIAGRAM

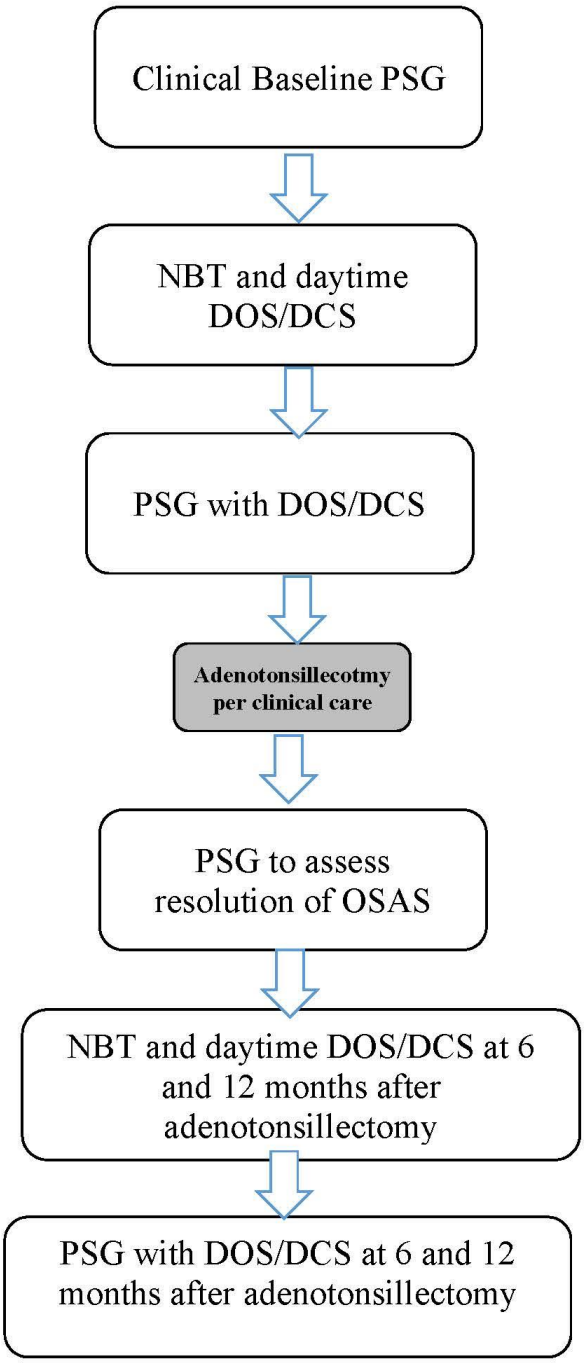
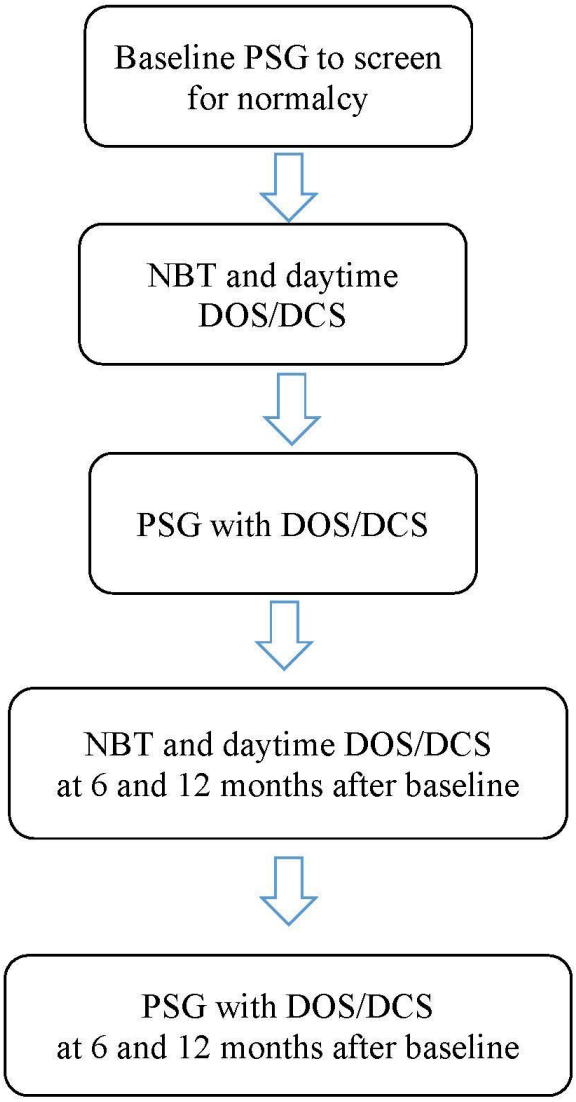


FIGURE 3: CONTROLS STUDY VISIT DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

The obstructive sleep apnea syndrome (OSAS) is common, affecting 2-3% of children.**(1)** It is associated with significant morbidity such as growth failure,**(2)** systemic,**(3-5)** and pulmonary hypertension, **(6, 7)** endothelial dysfunction,(8, 9) and cognitive and behavioral impairment.**(10)** This is important as the brain undergoes crucial development during childhood and thus, the long-term consequences of cognitive and behavioral dysfunction may have great impact in children's future adult life. Imaging studies of adults with OSAS have identified abnormal morphology of the frontal cortex, an important area for executive function.**(11, 12)** Other studies using magnetic resonance spectroscopy imaging have shown altered central nervous system metabolites of neuronal white and gray matter in adult and children with OSAS, which may be indicative of neuronal injury.**(13)** Researchers have hypothesized that this neuronal injury results in cognitive and behavioral consequences, and is caused by OSAS-associated hypoxemia. OSAS, however, is not only characterized by periods of hypoxemia. OSAS patients experience hypercapnia and frequent arousals from sleep as well, as a consequence of the repetitive episodes of upper airway obstruction that are the hallmark of OSAS.**(14, 15)** In fact, we have shown that children with OSAS, during wakefulness, have blunted CBF responses to hypercapnia compared to normal controls. (16)Therefore, the overall aim of this research protocol is to further delineate the mechanisms by which behavioral and cognitive dysfunction occur in children with OSAS based on our previous CBF findings. The overall hypothesis is that children with OSAS have abnormal Cerebral Blood Flow (CBF) regulation during wakefulness and sleep, manifested by blunted CBF response to hypercapnia that improves after treatment of OSAS. We further hypothesize that this CBF dysregulation correlates with the degree of behavioral and cognitive dysfunction.

1.2 Relevant Literature and Data

OSAS is a common problem in children,(1) and is associated with multiple long-term consequences. Its prevalence is likely to increase with the current obesity epidemic.(17-20) More and more children are being diagnosed with OSAS, and obese children are less likely to respond to simple surgical treatment (adenotonsillectomy), (21, 22) leaving more of them at risk for complications. One of the important complications of untreated OSAS are cognitive and neurobehavioral impairment.(10)

Nocturnal intermittent hypoxemia, hypercapnia and/or sleep fragmentation are potential pathogenic factors for the neurocognitive and behavioral dysfunction in patients with OSAS. Indeed, a pathophysiologic link between nocturnal recurrent hypoxemia and brain damage has been suggested by studies showing abnormalities of central nervous system white matter and cortical impairment in patients with OSAS, even in those without associated vascular risk factors. (23) Furthermore, studies in adults with OSAS, using techniques such as transcranial Doppler ultrasound, cerebral near-infrared spectroscopy (NIRS) and single photon emission computed tomography (SPECT), have shown significant alterations in central nervous system blood flow during both wakefulness and sleep.(24-26) Although results have

been varied, the most common finding is reduction of cerebral blood flow (CBF). Hayakawa *et al* showed that during apneic episodes there is a consistent decrease in oxyhemoglobin saturation in the cerebral tissue due to decreased oxygen supply, despite concomitant possible increase in CBF.(26) This finding suggests that during an apnea, the increased CBF cannot compensate for reduced oxygen arterial blood oxygen saturation. Moreover, this study showed a significant correlation between the decrease in oxyhemoglobin arterial saturation and the duration of apnea, suggesting that the cerebral hypoxia may become more severe with a prolonged apnea.

Diffuse optical and correlation spectroscopy (DOS and DCS) utilize near infrared light in order to noninvasively and continuously monitor intravascular hemodynamics in tissues, including the brain. Diffuse optical spectroscopy (DOS) quantifies total hemoglobin concentration (THC), which is proportional to cerebral blood volume (CBV), and tissue oxygen saturation (StO2). Diffuse correlation spectroscopy (DCS) quantifies relative changes in regional CBF by monitoring fluctuations of light interference patterns at the tissue surface caused by motion of red blood cells. When combined, the information from DCS and DOS can provide information about changes in cerebral metabolic rate of oxygen. Our co-investigator, Drs. Licht and his team have used a combined, non-invasive, optical brain imaging probe to measure DCS/DOS in multiple CHOP research studies, including studies in infants and children with congenital heart disease, stroke (CHOP IRB # 4357, 7551, 7986, 8442, 8443, 8347). In addition, Dr. Licht's team has previously collaborated with the P.I. of this proposal and used the same device on the pilot study that led to the current research (CHOP IRB # 9673).(16)

We plan to investigate the association between changes in CBF and regional tissue oxygenation during wakefulness and sleep in order to better understand the pathophysiology underlying behavioral and neurocognitive defects. We will measure DOS/DCS (CBF testing) in association with the neurocognitive and behavioral consequences of OSAS in children with OSAS and controls. We will later assess whether treatment of OSAS results in improved DOS/DCS in addition to improved cognition and behavior.

1.3 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56,. All episodes of noncompliance will be documented.

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

2 STUDY OBJECTIVES

The purpose of the study is to determine the relationship between cerebral blood flow regulation and neurobehavioral outcomes in children with OSAS.

2.1 Primary Objective (or Aim)

The primary objectives of this study are:

- To determine whether children with OSAS have impaired cerebral blood flow regulation elicited by hypercapneic challenge compared to normal controls, and whether this impairment correlates with cognitive and behavioral measurements.

2.2 Secondary Objectives (or Aim)

To determine whether this cerebral blood flow regulation impairment, and cognitive and behavioral measurements improve after treatment of OSAS.

Other secondary objectives are to determine the association between:

- Cerebral blood flow regulation and severity of OSAS.
- Cognitive and behavioral measurements and severity of OSAS.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is a prospective case-control study.

All participants who have not had a baseline sleep study performed within the prior 12 months to enrollment will undergo baseline polysomnography. For participants with OSAS, this will have been obtained as part of their clinical care unless they are referred via the CHOP PeRC system. In these cases, the baseline polysomnogram will be part of research simply to facilitate recruitment. Both OSAS and controls will then undergo cognitive and behavioral testing during wakefulness, and CBF testing during wakefulness and sleep at 3 time periods over 12 months approximately (figures 2 and 3). OSAS participants will also undergo a repeat baseline sleep study 6-12 weeks after clinical treatment to document improvement.

3.2 Study Duration, Enrollment and Number of Sites

Duration of study participation for the subject will be 12-14 months approximately.

We plan to enroll 70 subjects in each arm in order to have 50 evaluable subjects in each arm at the end of the study. This research will be carried out at one site only: Children's Hospital of Philadelphia.

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

3.3.1 Duration of Study Participation

3.3.1.1 Subjects with OSAS

The study duration is estimated at 12-14 months approximately. However, this will depend on the timing of treatment as they will undergo testing pre- and post-OSAS treatment. Their participation will entail a total of 8 visits:

Pre-treatment: The cognitive and behavioral, and CBF during wakefulness testing duration is one full day. The CBF nighttime testing is one full night.

Post-treatment: Six to twelve weeks after clinically indicated surgical treatment, OSAS participants will have a repeat baseline polysomnogram (one full night) to assess for residual OSA. Six and twelve months after the surgical treatment, the sleep study with the nighttime CBF testing, as well as the daytime neurobehavioral and CBF testing will be repeated to assess for changes.

3.3.1.2 Control Subjects

The study will include 7 total visits for controls: a baseline sleep study to ensure normalcy, three full days of cognitive and behavioral and CBF testing (baseline, 6 and 12 months), and three sleep studies with CBF testing (baseline, 6 and 12 months). A daytime visit and one night time visit may be scheduled during a 24-hour period if the participant and family wish so. Otherwise, they will be scheduled on separate days.

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

The study will be conducted at one investigative site only: Children's Hospital of Philadelphia.

Recruitment will stop when approximately 140 subjects are enrolled. It is expected that approximately 140 subjects will be enrolled to produce 100 evaluable subjects (50 in each arm).

3.4 Study Population

3.4.1 Inclusion Criteria (OSAS subjects)

Subjects with OSAS who fulfill the following clinical and polysomnographic criteria will be included:

(1) Age between 6 years and 12 years. The lower limit criterion was selected to include children who can understand and cooperate with testing. The upper limit criterion was selected to avoid overlap with the adult presentation of OSAS.

(2) Absence of neurologic, cardiovascular, pulmonary, or any other chronic illness with the exception of well-controlled asthma

(3) No prior surgery on the nose, palate or oropharynx including an adenotonsillectomy

(4) No current drug intake that may interfere with testing such as sedatives or stimulants

(5) No prior treatment of sleep-disordered breathing

(6) Polysomnographic recording criteria: subjects with OSAS must have an obstructive apnea hypopnea index (AHI) ≥ 5/hour and be a candidate for clinically-indicated surgical treatment.

(7) Parental/guardian permission (informed consent) and if appropriate, child assent.

3.4.2 Exclusion Criteria (OSAS Subjects)

(1) Previous adenotonsillectomy

(2) Previous use of CPAP

(3) Craniofacial anomalies that can interfere with upper airway anatomy (e.g., Treacher-Collins syndrome)

(4) Genetic syndromes (e.g., Trisomy 21, Prader-Willi)

(5) ADHD on medication

(6) Developmental delay as determined by receiving a score <70 on the ABAS-III.

(7) Non-English speaking participants due to the nature of neurobehavioral testing

3.4.3 Inclusion Criteria (Control subjects)

Control subjects who fulfill the following clinical and polysomnographic criteria will be included:

(1) Age between 6 years and 12 years. The lower limit criterion was selected to include children who can understand and cooperate with testing. The upper limit criterion was selected to avoid overlap with the adult presentation of OSAS.

(2) Absence of neurologic, cardiovascular, pulmonary, or any other chronic illness with the exception of well-controlled asthma

(3) No prior surgery on the nose, palate or oropharynx including an adenotonsillectomy

(4) No current drug intake that may interfere with testing such as sedatives or stimulants

(5) No prior treatment of sleep-disordered breathing

(6) Polysomnographic recording criteria: Normal control subjects must have an AHI ≤ 1.5/hour.

(7) Parental/guardian permission (informed consent) and if appropriate, child assent.

3.4.4 Exclusion Criteria (Control Subjects)

(1) Previous adenotonsillectomy

(2) Previous use of CPAP

(3) Craniofacial anomalies that can interfere with upper airway anatomy (e.g., Treacher-Collins syndrome)

(4) Genetic syndromes (e.g., Trisomy 21, Prader-Willi)

(5) ADHD on medication

(6) Developmental delay as determined by receiving a score <70 on the ABAS-III.

(7) Positive Pediatric Sleep Questionnaire

(8) Non-English speaking participants due to the nature of neurobehavioral testing

4 STUDY PROCEDURES

4.1 OSAS Participants

4.1.1 Screening Visit + Visit 1

The following procedures will be performed:

- Informed consent will be obtained before any study procedure/evaluations occur
- Review of inclusion/exclusion criteria
- Administer ABAS-III
- Demographics and medical history
- Mallampati/tonsillar size assessment
- Height and weight assessment
- OSAS participants will undergo a sleep study only if this has not been obtained clinically during the previous 12 months.
- OSAS participants will undergo a sleep study with CBF testing if a diagnostic sleep study has already been performed to confirm OSAS.

4.1.2 Visit 2: Daytime, 1 to 30 days after screening visit

- Mallampati airway score and tonsillar assessment
- Cognitive and behavioral testing
- CBF testing during wakefulness during hypercapneic ventilatory response

4.1.3 Visit 3: Post-Operative sleep study 6-12 weeks after adenotonsillectomy

- Sleep study to assess resolution of OSAS. If the post-operative AHI is ≥ 5 events per hour, participants will be referred to clinical care. However, they will continue in the study and perform procedures as planned. Data collected from such participants will be analyzed separately.
- Height and weight assessment.

4.1.4 Visit 4: Daytime, 6 months after adenotonsillectomy

- Cognitive and behavioral testing
- CBF testing during wakefulness during hypercapneic ventilatory response

4.1.5 Visit 5: Nighttime, 6 months after adenotonsillectomy

- CBF testing during sleep during hypercapneic ventilatory response

- Height and weight assessment

4.1.6 Visit 6: Daytime, 12 months after adenotonsillectomy

- Cognitive and behavioral testing
- CBF testing during wakefulness during hypercapneic ventilatory response

4.1.7 Visit 7: Nighttime, 12 months after adenotonsillectomy

- CBF testing during sleep during hypercapneic ventilatory response
- Height and weight assessment

4.2 Control Participants

4.2.1 Screening Visit (Visit 1)

- Informed consent will be obtained before any study procedure/evaluations occur
- Review of inclusion/exclusion criteria
- Administer ABAS-III
- Demographics and medical history
- Height/weight assessment Baseline sleep study to rule out OSA

4.2.2 Visit 2: Daytime, 1 to 30 days after screening visit

- Mallampati airway score and tonsillar assessment
- Cognitive and behavioral testing
- CBF testing during wakefulness during hypercapneic ventilatory response

4.2.3 Visit 3: Nighttime, 1 to 30 days after screening visit

- Height/weight assessment
- CBF testing during sleep during hypercapneic ventilatory response

4.2.4 Visit 4: Daytime, 6 months after Visit 1

- Cognitive and behavioral testing
- CBF testing during wakefulness during hypercapneic ventilatory response

4.2.5 Visit 5: Nighttime, 6 months after Visit 2

- Height/weight assessment
- CBF testing during sleep during hypercapnic ventilatory response

4.2.6 Visit 6: daytime, 12 months after Visit 1

- Cognitive and behavioral testing
- CBF testing during wakefulness during hypercapneic ventilatory response

4.2.7 Visit 7 Nighttime, 12 months after Visit 1

- Height/weight assessment
- CBF testing during sleep during hypercapnic ventilatory response

4.3 Monthly Telephone Calls

- There will be telephone calls during each month that a visit into the hospital is not necessary (months 2, 3, 4, 5, 7, 8, 9, 10, 11) for retention purposes, as well as to assess to for adverse events.

4.4 Unscheduled Visits

Occasionally, due to technical issues arising from the complex set up necessary for NIRS data collection, the data may not be optimal. Therefore, we will need to recollect CBF data during wakefulness from some subjects. In these cases, we will contact them asking their permission to be retested. Those who agree will be re-consented and receive the standard stipend for the daytime testing.

4.5 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to inability to follow instructions and perform testing. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.5.1 Early Termination Study Visit

Subjects who withdraw from the study will be referred for clinical care.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

The following procedures will be performed:

- Demographics: age, gender, race

- Review of inclusion/exclusion criteria
- Previous PSG, if available.

5.1.2 Physical Examination

- Mallampati airway classification and tonsils size will be collected.
- Height
- Weight
- Vital signs

5.1.3 Other Evaluations, Measures

- **Baseline Polysomnography:**

Baseline polysomnography will be performed as part of the routine clinical evaluation of the subjects with OSAS prior to study entry (as per routine clinical practice), and as part of the research protocol in controls and OSAS subjects post-adenotonsillectomy. Overnight polysomnography will be performed in a dedicated pediatric sleep laboratory. The following parameters will be recorded (using Rembrandt, Medcare, Buffalo, NY): electroencephalogram, electrooculogram, submental and tibial electromyograms, chest and abdominal wall movement by inductance plethysmography (Respitrace, Ambulatory Monitoring Inc., Ardsley, NY); ECG; airflow by nasal pressure (Pro-Tech, Mukilteo, WA) and 3-pronged thermistor (Pro-Tech), end-tidal PCO_2 (Novametrix 7000; Novametrix, Wallingford, CT); arterial oxygen saturation (Masimo, Irvine, CA or Nonin, Plymouth, MN) and digital, infra-red video. The infra-red video is a component of any sleep study that is crucial for polysomnography interpretation as it provides information on breathing patterns, parasomnias, movements and seizures. The following parameters will be determined using standard pediatric techniques and scoring. (27). Any and all video recording will be in accordance with CHOP's policy on recording or filming patients.

1. Sleep architecture
2. Apneas and hypopneas
3. Arterial oxygen saturation (S_pO_2)
5. End-tidal carbon dioxide tension ($ETCO_2$)

- Diffuse optical and correlation spectroscopy (DOS/DCS): The apparatus consists of light sources and detectors which are embedded in a rectangular black rubber pad that is strapped to the subject's head (similar to a pulse oximeter probe). The rectangular probe will be shielded from room light by a small disposable black cloth. For DOS, the static optical properties (absorption and reduced scattering coefficients) of the brain tissue will be measured using 110 MHz diffuse photon density waves at 690 and 830nm. From the absorption coefficients at these two wavelengths, we will obtain average cerebral oxygen saturation and total hemoglobin

concentration. Measurements will be made over the frontal cortex, and based on our probe geometry, light will penetrate approximately 0.5 cm into the brain. For DCS, the static optical properties will be measured by NIRS with 70 MHz diffuse photon density waves at 690, 786 and 830nm. Monitoring the absorption coefficient at the three wavelengths follows the hemoglobin saturations. Changes in CBF are obtained from correlation of decay times. The complete sets of source detector measurements provide both average values and local values of the tissue blood dynamics. DOS/DCS is a non-significant risk device as defined by Food and Drug Administration (FDA) and therefore does not require FDA approval for investigational use. The device is used to collect data and is not being tested a part of the protocol. The instrument has been approved for laser and electrical safety by the University of Pennsylvania Environmental Health and Radiation Safety department and both CHOP and HUP clinical engineering departments for electrical safety. The optical imaging device will be used to record left and right hemispheric CBF, THC, and StO_2. These three measurements will be performed continuously during the study time. The CBF measurements for each hemisphere (separately), THC and StO_2 measurements from the last four minutes of each five minute recording interval will be averaged to avoid potential transient effects. This averaged number for right CBF, left CBF, and StO_2 will be used in the statistical analysis.

- Ventilatory Response Testing during wakefulness: Ventilatory responses to hypercapnia will be determined using the rebreathing technique.(28-30) This is a standard clinical test. A physician will be present throughout the testing. Participants will sit quietly for 5-10 minutes before testing. Testing will be performed with the subject seated comfortably, watching a video, and breathing through a mouthpiece. Heart rate, SpO_2 and end-tidal CO_2 will be monitored continuously. Flow will be measured using a heated pneumotachograph connected to the mouthpiece and a differential pressure transducer. The actual test takes < 5 minutes but setup may take a total of about 30 minutes.

    - Ventilatory response to hypercapnia will be determined using the rebreathing technique of Read.(29) At the end of a normal expiration, a valve will be turned so that the subject will begin to breathe from a 13-liter bag. The bag will be filled with 70 ml/kg of a gas mixture with the initial composition of 95% O_2 and 5% CO_2. Each test will be continued until the subject cannot continue or end-tidal PCO_2 reaches 65-70 mm Hg. Each test will be completed within 4-5 minutes to avoid prolonged respiratory acidosis. Tests will be discarded if the subject comes off the mouthpiece before the PCO_2 reaches 55 mm Hg. Heart rate, SpO_2, oximeter pulse waveform, and end-tidal PCO_2 will be monitored continuously. The duration of this test is about 5 minutes.

- Ventilatory response testing during sleep: Subjects will wear a snug orofacial CPAP mask that will be attached to a heated pneumotachometer (Hans Rudolph, Kansas City, MO) and transducer (Validyne Engineering, Northridge, CA) and then to a T circuit. OSAS participants will receive an individualized positive pressure aimed at

treating obstructive sleep apnea and controls will receive a holding pressure of 2 cm H_2O.(31) Room air will flow through the CPAP flow. $ETCO_2$ will be measured via a port in the mask with an infrared capnometer (Novametrix 7000; Novametrix, Wallingford, CT). Transcutaneous CO_2 (Radiometer, Paramus, NJ) will be continuously monitored during the study. A constant flow of CO_2 will be introduced into the circuit at 5 l/min until the PCO2 reaches 65 mm Hg, the patient arouses, or for a maximum of 3 min, whichever occurs first. There will be no change in the total flow as air bias flow will be self-adjusted by the CPAP machine. Between challenges, subjects will breathe room air for a minimum of 15 min after the return of SpO2 and $ETCO_2$ to baseline. Challenges will be primarily performed in slow-wave sleep (SWS); when possible, they will be repeated during stage 2 and rapid-eye-movement (REM) sleep. One trial will be attempted in each sleep stage. A physician will be in constant attendance at the bedside, and the patient's heart rate, respiration, and gas exchange will be closely monitored.

- Cognitive and Behavioral measures:

    - Participants will undergo the following testing:
        - Conners Continuous Performance Test-II (CPT-III)
        - Digit Span subtest of the Wechsler Intelligence Scale for Children, 4th Edition.
        - Tests of Everyday Attention for Children (TEA-ch)
        - Purdue Pegboard Test
        - Behavioral Rating Inventory of Executive Function -- Child Version (BRIEF-2)
        - Child Behavior Checklist
        - Epworth Sleepiness Scale Modified for Children
        - Adaptive Behavior Assessment System, Third Edition (ABAS-III)

5.2 Safety Evaluation

During the sleep study, arterial oxygen saturation using pulse oximetry, transcutaneous carbon dioxide tension, EEG and EKG will be continuously monitored, and the patient will be visualized via a video camera.

During CBF measurements with ventilatory responses, heart rate, pulse oximetry, transcutaneous carbon dioxide tension, and end-tidal CO_2 measurements will be continuously monitored and the patient will be directly visualized. A physician will be present whenever CO_2 is administered.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint is the cerebral blood flow change in OSAS subjects compared to controls during hypercapneic challenge and its correlation with behavioral and cognitive testing results.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- The change in cerebral blood flow regulation in OSAS subjects before and after treatment of OSAS at 6 months
- The change in behavioral and cognitive testing results before and after treatment of OSAS at 6 and 12 months
- The association between cerebral blood flow regulation and severity of OSAS at baseline and its changes at 12 months.

6.3 Control of Bias and Confounding

The co-investigator performing the neurocognitive testing will be blinded to the subjects' condition (OSAS or controls).

6.4 Statistical Methods

6.4.1 Baseline Data

Descriptive analyses will consist of frequencies for categorical variables, mean, median, range, standard deviation (SD), standard error of the mean (SEM) for continuous variables, and 95% CI of the means and of the medians (for skewed distributions). Demographic variables will be compared between groups at baseline using the t-test or Wilcoxon rank sum test (for continuous variables) or the X2 test (for categorical variables). The distributions of outcomes will be assessed via graphical checks and tests for normality. If necessary, transformations (e.g., log) will be applied to improve normality and skewed data.

6.4.2 Analysis of Primary Outcome of Interest

The primary analysis will include all subjects meeting all inclusion and exclusion criteria and completing all study visits.

The primary endpoint will be the change in CBF in OSAS and controls at baseline.

The secondary endpoint will be the change in CBF in OSAS and controls at 6 and 12 months after baseline measurements for controls and after adenotonsillectomy for OSAS.

Longitudinal models using generalized estimating equations (GEE) will be fitted to explore effects of treatment on CBF and NBT. An indicator variable for treatment, time, and a time by treatment group interaction term will be included in the models. If the interaction term

differs significantly from zero, this will indicate that the change over time in the outcome of interest differs significantly between the two groups. We will assess the sensitivity of results to the choice of working correlation structure that models association in the GEE analyses. We will also implement quasi-least squares (QLS), an approach based on GEE that allows for implementation of the Markov correlation structure.(32) The Markov structure is plausible if participants have unequal temporal spacing of their measurements. In addition, we will consider the application of mixed effects models if the assumptions of these models are met. An indicator variable for subjects who resolve after treatment versus those who do not resolve after treatment will be included in the model to account for those children whose OSAS may not resolve after surgery.(22, 33, 34) Pre-, post treatment change in AHI will be included in the model, and potential confounding variables such as age, gender, race, socio-economic status and BMI will also be included in the models.

Hypercapnic ventilatory responses will be controlled for BMI as obese participants may have different responses compared to non-obese participants.

6.5 Sample Size and Power

A sample size of 50 in each group (total N = 100) will have 80% power to detect a moderate effect size of 0.566 using a two group t-test with a 0.05 two-sided significance level. We plan to recruit 70 in each group to account for attrition.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

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

7.2 Adverse Event Reporting

All on-site SAEs (CHOP or related sites) will be reported to the IRB in accordance with CHOP IRB policies. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

7.3 Definition of an Adverse Event

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

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

7.4 Definition of a Serious Adverse Event (SAE)

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

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

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

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

7.4.1 Relationship of SAE to study drug or other intervention

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

7.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

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

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days

Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

7.5.1 Follow-up report

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

7.6 Investigator Reporting of a Serious Adverse Event to Sponsor

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

7.7 Medical Emergencies (if applicable)

Conditions that will generate and Urgent Medical Referral (UMRA) are those laboratory, physiological or behavioral findings that are believed to represent conditions that may require additional evaluation by the participant's health care providers in a timely manner. Thus, if these conditions are identified during the course of the study, their occurrence will generate an Urgent Medical Referral by the PI who will communicate with the participant's guardian, and with his permission will contact the child's primary care provider. These conditions include:

- Subjects with significant hypoxemia on polysomnography (> 10% of total sleep time with $S_pO_2 < 75\%$)
- Subjects with severe OSAS-related arrhythmias on polysomnography.

8 STUDY ADMINISTRATION

8.1 Data Collection and Management

1. Confidentiality. Data will be stored in a password-protected file stored on the sleep secure research server. Sleep study data will be backed up on CD/DVDs and stored in a locked cabinet. The video recordings are part of the sleep study, and as such they will be kept forever, stored in a locked office in the sleep lab with restricted access.

2. Security. Data will be backed up in Redcap as a copy of the password-protected file on the PI's office computer.

3. Anonymization, de-identification or destruction. The identifiers will be destroyed after publication. However, identifiers of subjects who have agreed to be contacted for future research will be kept in a password protected file. The other data will be retained forever. Our laboratory maintains a locked cabinet specifically for such archives.

8.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Research data and records will be saved as password-protected computer files. Patient identifiers will be removed. Data will be stored indefinitely. The Investigators will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

8.3 Regulatory and Ethical Considerations

8.3.1 Data and Safety Monitoring Plan

- Principal Investigator: It is the responsibility of the Principal Investigator to oversee the overall safety of the study. This will include careful assessment and appropriate reporting of adverse events. The PIs responsibility will be to assure that appropriate study data are communicated to the participant's family and physicians and that appropriate referrals or interventions are initiated. He will discuss AEs with the medical monitor and report them to the IRB, DSMB and NIH when appropriate.

- Medical Monitor: Suzanne Beck, MD will be the medical monitor with whom the team will discuss AEs. She is otherwise unrelated to the research protocol and will not perform research procedures, as mandated by NHLBI.

- Data Safety Monitoring Board (DSMB): The study will have a Data Safety Monitoring Board (DSMB) as mandated by NHLBI. The DSMB will be responsible for overall participants' safety during the study. DSMB members are experts in their field, have bioethical experience in conducting research in children, and are unrelated to this research. The DSMB will be comprised of:

    - Ranaan Arens, M.D. Professor of Pediatrics, Albert Einstein College of Medicine. Chief, Division of Respiratory and Sleep Medicine, Montefiore Medical Center. Dr. Arens is the external member of the DSMB.

    - Adva Buzi, MD, Attending Physician, Division of Otolaryngology, The Children's Hospital of Philadelphia

- Justine Shults, Ph.D. Biostatistician. The Children's Hospital of Philadelphia Clinical and Translational Research Center.

- The DSMB will meet twice a year and as needed. The meetings will be held via teleconference. Serious adverse events and unanticipated events will be reported according to NHLBI policies. Once a month, the DSMB will receive reports of all adverse events (AE). On a quarterly basis, or more frequently if needed, summary reports of all AEs will be provided to the DSMB. For each DSMB meeting, reports will be provided. These will include data on recruitment and baseline characteristics, completeness of follow-up, and analyses of AEs. Justine Shults, PhD, the study statistician, will prepare these reports. The reports will provide information that is accurate, with follow-up that is complete to within one month of the date of the DSMB meeting. The reports will be provided to DSMB members approximately one week prior to the date of the meeting. Minutes for each meeting will be prepared.

8.3.2 Risk Assessment

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

Diffuse optical and correlation spectroscopy: Not greater than minimal risk. The hybrid DOS/DCS instrument is considered a non-significant risk device. There has been experience at both CHOP and The Hospital of the University of Pennsylvania with the instrument, and there have been no AEs. Please see attached safety notes.

Psychometric Testing: Not greater than minimal risk. This testing is potentially stressful or anxiety-producing; these risks will be addressed by offering breaks from testing as needed and having examiners who are well-trained in testing children and adolescents. Testing will be conducted in an appealing and quiet private area with child-sized furniture.

Hypercapneic challenge: Not greater than minimal risk. During wakefulness, the measurement of carbon dioxide and hypoxic responses may make the participant feel short of breath, as if he/she was running. Rarely, the participant may have a headache or dizziness from increased carbon dioxide. This will go away quickly after the test or after coming off the mouthpiece. The subject can come off the mouthpiece if he/she is uncomfortable. During sleep, these tests may cause arousal; typically, the subject is unaware of the cause of the arousal, and rapidly returns to sleep. If the participant is uncomfortable, s/he simply needs to remove the mask in order to breathe room air. The test will be stopped if the subject has frequent arousals, defined as waking from sleep more than 3 times during the hypercapneic challenge). A physician will be present whenever CO_2 is administered, and the subject's end-tidal and transcutaneous PCO_2, arterial oxygen saturation, EKG and EEG will be continuously monitored. Sleep disruption from arousals may result in excessive daytime sleepiness, inattention and impaired vigilance the following day. These effects are transitory and resolve with a good night of sleep. (35) Therefore, participants should not take school tests the following day.

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

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

8.3.3 Potential Benefits of Study Participation

There will probably be no direct benefits to the individual subject. Subjects with OSAS may benefit from the follow-up polysomnography to evaluate their treatment. Control subjects may benefit if unsuspected abnormalities are detected on polysomnography.

8.3.4 Risk-Benefit Assessment

The risks of this study are not greater than minimal. Although participating subjects may not obtain direct benefit, data from this study will help better understand the pathophysiology of OSAS, so that ultimately we can develop better forms of prevention and of treatment.

8.4 Recruitment Strategy

Subjects with OSAS will be recruited from the Sleep Center at the Children's Hospital of Philadelphia. The Sleep Center is composed of both a Sleep Clinic and Sleep Laboratory. The multidisciplinary Sleep Clinic (pediatric pulmonology, neurology and psychology) evaluates approximately 2,000 pediatric subjects with varying sleep disorders each year; approximately half of these are referred for polysomnography.

All the care providers at the Sleep Clinic will be informed of this study. If the prospective subjects are not patients of this study's P.I., they will be notified of this study by their physician. If the subjects are interested in the study, they will be referred to us. We will also screen the results of the polysomnograms performed in the Sleep Laboratory for clinical purposes to identify more eligible subjects with OSAS. We will approach the eligible subjects with OSAS to discuss this study. In addition, we will set up a PeRC prompt in the CHOP system to facilitate the referral of children with suspected OSAS. Our team will coordinate the sleep study of these children.

Controls will be recruited from the community based in advertisements in newspaper/magazine.

The study team will also utilize the services of the Recruitment Enhancement Core (REC). The REC provides assistance with recruitment plan development and may assist in identifying and contacting potential participants using the Clinical Reporting Unit (CRU), the CHOP Recruitment Registry, social media and internal communication resources. The REC also engages community partners and facilitates outreach on behalf of the research Institute and CHOP research studies.

The investigators will abide by IRB SOP 15, which states that "Employees, volunteers (ie; NTP) and their immediate families may not participate in research studies within a division in which they work or are assigned, unless a waiver is granted from the IRB Chair (such as for treatment studies).

The flyer that is currently attached to the eIRB application will be the only form of print material used for newspaper and/or magazine ads.

The Research Creative Institute has also developed a flyer to be distributed to patients which will be given to possible participants for information purposes.

8.5 Informed Consent/Assent and HIPAA Authorization

One of the study investigators will be responsible for obtaining informed consent/assent. Informed consent will be obtained from the parents/legal guardians of the subjects, and assent from subjects who are 7 years and older. Informed consent/assent will be obtained before this research study. The consent/assent process will take place in a private room and parents/subjects will be given unlimited time to decide their participation. Parents/subjects will be asked to explain back to the investigators the nature of the study, study procedures and the risks and benefits of participation to assure their understanding. A combined consent-authorization document will be utilized.

8.6 Payment to Subjects/Families

Please note that the dollar amount to be received by families per calendar year will not exceed $600. For example, a control participant coming for visit 1 on January 2, 2017 will end his/her participation on or after January 2, 2018.

8.6.1 Compensation

The caregiver accompanying the child to the sleep study will receive $50 for each sleep study performed (total =$200 for the entire study for controls. OSAS participants will receive $250 total if the initial study was performed as part of research and $200 if it was performed as part of clinical care) as a compensation for time and effort. The caregiver accompanying the child to daytime testing will receive $37.50 (total =$112.5 for the entire study) for daytime testing (NIRS and behavioral testing) as compensation for time and effort. Payments to parent for time and inconvenience (i.e. compensation)

Parents will not be paid for time and inconvenience.

8.6.2 Payments to subject for time, effort and inconvenience (i.e. compensation)

Children will be paid $50 as compensation for time and effort for sleep study (total =$200 for the entire study for controls. OSAS participants will received $250 total if the initial study was performed as part of research and $150 if it was performed as part of clinical care). In addition, children will receive $37.50 (total =$112.5 for the entire study) as compensation for time and effort during daytime testing.

8.6.3 Gifts

Stickers and small prizes (less than $5 each) will be given to the children.

9 PUBLICATION

It is anticipated that the completed study will be submitted for publication to a peer-reviewed medical journal.

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APPENDIX

All neurobehavioral measures are included in CHOP's IRB's Validated Instruments Library.