Title:	**Utility of nasal steroids for treatment of childhood obstructive sleep apnea**
Short Title	SPARK (steroid treatment for apnea research study)
Drug or Device Name(s):	XXXXX
FDA IND	N/A
Regulatory Sponsor:	
eIRB Number	10942
Protocol Date:	July 18, 2014

Amendment 1 Date: July 18, 2014

Amendment 2 Date: August 13, 2014

Amendment 3 Date: September 26, 2014

Amendment 4 Date: October 24, 2014

Amendment 5 Date: March 4, 2015

Amendment 6 date: May 07, 2015

Amendment 7 Date: September 15, 2015

Amendment 8 Date: January 21, 2016

Amendment 9 Date: October 10, 2016

Amendment 10 Date: May 2, 2017

Amendment 11 Date: December 14 , 2017

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AHI	Obstructive apnea hypopnea index
AT	Adenotonsillectomy
CPAP	Continuous positive airway pressure
NCS	Nasal corticosteroids
OSA	Obstructive sleep apnea syndrome
PSG	Polysomnogram

ABSTRACT

Context:

The childhood obstructive sleep apnea syndrome (OSAS) is very common, occurring in 1-3% of otherwise healthy children. If untreated, it can result in significant morbidities. Current treatment of childhood OSAS is primarily surgical (i.e., adenotonsillectomy, AT), with continuous positive airway pressure (CPAP) and other medical measures being used much more rarely. Several studies have suggested that nasal corticosteroids (NCS) may be effective in the treatment of childhood OSAS. However, the utility of NCS in children with OSAS has not been fully evaluated.

Objectives:

Primary Objective: To determine the efficacy of NCS *vs.* placebo in treating OSAS in children.

Secondary Objectives:

-To determine which factors modify the response to NCS

-To determine the long-term effect of NCS vs. placebo in the treatment of OSAS in children

-To determine the side-effects associated with chronic NCS use in children with OSAS

Study Design: Randomized, parallel, double-blind, placebo-controlled study.

Setting/Participants: Single site study to be performed at CHOP. Participants will be recruited from outpatient offices and all procedures will be performed during outpatient research visits. 318 children aged 5-12 years with mild to moderate OSAS will be recruited.

Study Interventions and Measures:

Participants will be randomized to a 3-month course of nasal fluticasone or placebo. Both groups will undergo the following procedures at baseline and 3 months: history and physical exam, sleep study, pediatric sleep questionnaire, nasal symptoms questionnaire, quality of life questionnaire, neurobehavioral testing, acoustic reflectance airway measurement, spirometry, percutaneous skin allergy test, nasal secretions genetic expression profile, nasal secretions biomarkers, blood work for systemic biomarkers, cortisol, DHEAS, and ACTH levels, ophthalmology exam, knee height measurement and DXA scan. Families will keep an infection log. At the 3 months visit, participants in the NCS group will be further randomized to 9 months of NCS or placebo. All measurements will be repeated at the end of this 9-month period.

The primary study outcome measure is the change in OSAS severity measured by the obstructive apnea hypopnea index (AHI) 3 months after randomization.

PROTOCOL SYNOPSIS

Study Title	**Utility of nasal steroids for treatment of childhood obstructive sleep apnea**
Funder	NHLBI
Clinical Phase	N/A
Study Rationale	• The childhood obstructive sleep apnea syndrome (OSAS) is very common, occurring in 1-3% of otherwise healthy children. If untreated, it can result in significant morbidity. • *In vitro*, nasal corticosteroids (NCS) have been shown to reduce tissue proliferation and increase apoptosis in adenotonsillar tissue. These studies provide biologic plausibility for the use of NCS in the treatment of children with OSAS and adenotonsillar hypertrophy. • Current treatment of childhood OSAS is primarily surgical (i.e., adenotonsillectomy, AT), with continuous positive airway pressure (CPAP) and other medical measures being used much more rarely. AT is efficacious but residual OSAS often remains, and CPAP use is limited by poor adherence. • Several studies have suggested that NCS may be effective in the treatment of childhood OSAS. However, these studies have been limited by factors such as small size, lack of randomization and blinding, short-term follow-up, involvement of children with only very mild OSAS, and/or lack of stratifying for the presence of atopy. • We therefore plan a randomized controlled trial evaluating the efficacy and safety of NCS *vs.* placebo in children with mild to moderate OSAS. ***Our overall hypothesis is that NCS will be safe and efficacious in the treatment of mild to moderate childhood OSAS, particularly in children with asthma/atopy, but will require ongoing maintenance therapy.***
Study Objective(s)	**Primary** To determine the efficacy of NCS *vs.* placebo in treating OSAS in children **Secondary** • To determine which factors modify the response to NCS • To determine the long-term effect of NCS vs. placebo in the treatment of OSAS in children

	• To determine the side-effects associated with chronic NCS use in children with OSAS
Test Article(s) *(If Applicable)*	• Fluticasone nasal spray (55 mcg [one spray] per nostril daily) is chosen as *in vitro* studies have shown that is has greater potency in reducing adenotonsillar cellular proliferation than budesonide or dexamethasone. • Fluticasone is FDA-approved for the study age group. The Investigational Drug Service will prepare blinded nasal spray bottles with a metered pump (to deliver 55 mcg/0.1mL or placebo/0.1mL per pump) with a 30 day supply of solution per bottle.
Study Design	• Randomized, parallel, double-blind, placebo-controlled study.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Subjects age 5-12 years. 2. Mild to moderate OSAS, defined as an obstructive apnea index (AI) of 1-20/hr of total sleep time (TST) or AHI 2-30/hr of TST. 3. Parent-related symptoms of habitual snoring (>3 nights per week). 4. No history of adenotonsillectomy or prior NCS use. **Exclusion Criteria** 1. Severe OSAS or significant hypoxemia or hypercapnia on polysomnography (PSG), such that definitive treatment should not be delayed (AHI > 30/hr, more than 2% total sleep time with SpO_2 <90%, end-tidal PCO_2 > 60 mm Hg for $\geq$ 5 minutes, pathologic arrhythmias). 2. History of recurrent throat infections 3. Any NCS use in the past 3 months, or NCS use for $\geq$ 2 weeks in the past year 4. Abnormalities on baseline safety screening tests 5. Previous adenotonsillectomy 6. Previous adenoidectomy unless adenoidal tissue has been documented to have regrown 7. CPAP therapy 8. Pregnancy
Number Of Subjects	• 318 children will be recruited at CHOP. This is a single center study

Study Duration	• The participation of subjects randomized to the placebo group at the baseline visit will be 3 months. • The participation of subjects randomized to the NCS group at the baseline visit will be 12 months. • The entire study is expected to last 5 years
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: screening for eligibility and obtaining consent and (2) Intervention: Randomization: placebo or NCS for 3 months (3) Follow-up: randomization of NCS group to placebo or continuation of NCS for 9 months
Efficacy Evaluations	Change in AHI in the placebo and NCS groups at 3 months of therapy; and at 12 months of therapy
Pharmacokinetic Evaluations	N/A
Safety Evaluations	Worsening symptoms of OSAS, such as daytime sleepiness or development of complications, such as failure to thrive,
Statistical And Analytic Plan	• It is assumed that 50% of subjects will fail the baseline screening PSG. Thus, 318 subjects will be recruited initially. • 159 eligible subjects will be randomized in a 2:1 fashion to NCS *vs.* placebo, respectively; the initial group sizes will therefore be 106 NCS *vs.* 53 placebo subjects. The 2:1 randomization ratio is to allow for further randomization during the follow-up phase of the study. Based on our past studies we will assume a drop-out rate of 5% at 3 months. Therefore, the available sample size for analysis for Aim 1 will be 100 NCS *vs.*50 placebo subjects. • All analyses will be conducted with Stata 13.0, with two-sided tests of hypotheses and a p-value < 0.05 as the criterion for statistical significance. • Analyses will be conducted according to the intent to treat principle, with subjects analyzed according to their initial treatment assignment. • Descriptive analyses will include computation of means (with 95% confidence intervals), standard deviations, medians, interquartile-ranges (IQR) of continuous variables and tabulation of categorical variables. • A two-group t-test for independent samples or Wilcoxon rank sum test will be used to test the primary hypothesis that

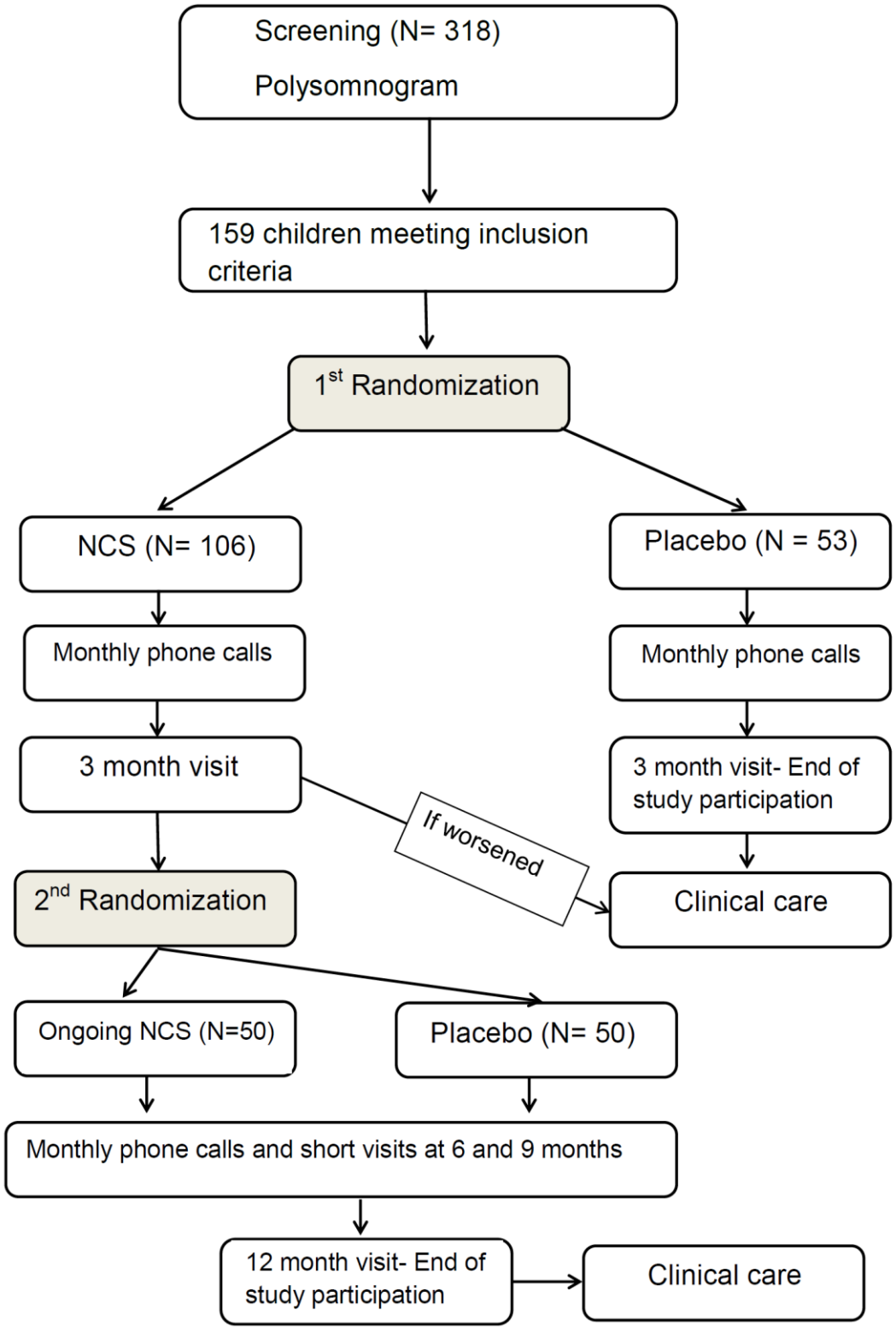
	the changes in AHI are equal between the two treatment groups.
DATA AND SAFETY MONITORING PLAN	Participants' data will be closely monitored by an external Data Safety Monitoring Board (DSMB) and an external safety officer. They will monitor adverse events and treatment failures.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screen**	**Treatment/Intervention**				**Follow-up**								
Visit Number		**Visit 1**	**Phone Contact 1**	**Phone Contact 2**	**Visit 2**	**Phone Contact 3**	**Phone Contact 4**	**Visit 3**	**Phone Contact 5**	**Phone Contact 6**	**Visit 4**	**Phone Contact 7**	**Phone Contact 8**	**Visit 5**
Study Days		**0**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**365**
Informed Consent/Assent	X													
Review Inclusion/Exclusion Criteria	X													
Demographics/Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X												X
Vital Signs: BP, HR		X			X			X			X			X
Height and Weight	X	X			X			X			X			X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep Study	X				X									X
Cognitive and Neurobehavioral testing		X			X									X
Quality of life questionnaires		X			X									X
Symptoms questionnaires		X			X			X			X			X
Airway measurement		X			X									X
Spirometry		X												

Percutaneous skin allergy test		X											
Blood tests		X			X								X
Ophthalmology exam		X			X								X
Nasal secretion testing		X			X								X
DXA scan		X			X								X
Urine pregnancy test		X			X								X
Randomization		X			X								
Dispense Study Drug		X			X								
Drug Compliance					X			X			X			X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X

FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

The childhood obstructive sleep apnea syndrome (OSAS) is defined as a "disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns (1)." It is very common, occurring in 1-3% of otherwise healthy children (2). If untreated, it can result in significant morbidity, including cognitive deficits, behavioral abnormalities, poor growth, hypertension, cardiac hypertrophy and metabolic derangements (2).

Current treatment of childhood OSAS is primarily surgical (i.e., adenotonsillectomy, AT), with continuous positive airway pressure (CPAP) and other medical measures being used much more rarely (3). AT is efficacious but residual OSAS often remains (4, 5). Furthermore, this invasive treatment is expensive, sometimes refused by families (6), and is associated with morbidity (7). CPAP use is limited by poor adherence (8). Thus, efficacious alternative or adjunct medical treatments would be highly desirable. Several studies have suggested that NCS or leukotriene antagonists may be effective in the treatment of childhood OSAS. However, these studies have been limited by factors such as small size, lack of randomization and blinding, short-term follow-up, involvement of children with only very mild OSAS, and/or lack of stratifying for the presence of atopy. We therefore plan a randomized controlled trial evaluating the efficacy and safety of NCS vs placebo in children with mild to moderate OSAS. Our overall hypothesis is that NCS will be safe and efficacious in the treatment of mild to moderate childhood OSAS, particularly in children with asthma/atopy, but will require ongoing maintenance therapy.

1.2 Name and Description of Investigational Product or Intervention

Participants will be randomized to fluticasone nasal spray that is FDA-approved for the study age group. Fluticasone nasal spray (55 mcg [one spray] per nostril daily) is chosen as *in vitro* studies have shown that is has greater potency in reducing adenotonsillar cellular proliferation than budesonide or dexamethasone (9). The Penn Investigational Drug Service will prepare blinded nasal spray bottles with a metered pump (to deliver 55 mcg/0.1mL or placebo/0.1mL per pump) with a 30 day supply of solution per bottle.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

In vitro studies have shown increased glucocorticoid receptor expression in adenotonsillar tissue, with increased glucocorticoid receptor alpha mRNA expression and increased leukotriene cysteinyl receptors LT1-R and LT2-R in adenoid/tonsillar tissue from children with OSAS compared to those with recurrent pharyngitis (10, 11). In vitro, nasal

corticosteroids (NCS) have been shown to reduce tissue proliferation, increase apoptosis and decrease the production of tumor necrosis factor-alpha and interleukins 6 and 8 in adenotonsillar tissue (9, 12). These studies provide biologic plausibility for the use of NCS in the treatment of children with OSAS and adenotonsillar hypertrophy.

1.3.2 Clinical Studies

1.3.2.1 Clinical Studies in Children

Studies of NCS treatment of OSAS have been limited by small sample size, lack of placebo control, limited duration, and variability in baseline data (11, 13-16). However, these limited data suggest that there is a benefit from NCS. A very small study of oral prednisone in 9 children showed a nonsignificant improvement in OSAS (14), and most studies of NCS have shown significant effects. Only two of the NCS studies were randomized and placebo controlled, of which one study was very small. The larger study evaluated children with mild OSAS only (AHI < 7/hr). All previous studies of NCS were very short-term, although one showed persistence of effects 8 weeks after treatment (13). The current study will examine both the short-term and the long-term impact of NCS. No studies have evaluated the efficacy of NCS in the subset of children with OSAS and atopy/asthma. No studies have evaluated the side-effects of chronic NCS use in the OSAS population.

1.4 Selection of Drugs and Dosages

Fluticasone nasal spray (55 mcg [one spray] per nostril daily) will be used. This is the only form available of this non-investigational drug, and the usual clinical dosage for this age group.

1.5 Relevant Literature and Data

Need for additional therapies for childhood OSAS: AT is the primary treatment for childhood OSAS. AT is the 2nd commonest surgical procedure performed in children, with > 580,000 performed annually in the USA, predominantly for airway obstruction (17). At an estimated cost of $5,442 each (18), the costs of surgery alone exceed $3.2 billion a year in the USA. AT can result in significant adverse events, including pain, dehydration, hemorrhage (3% of patients), post-operative respiratory compromise (~25% of patients with OSAS (26, 27), nasopharyngeal stenosis, velopharyngeal incompetence and death (2). Although the surgery is generally effective, studies have shown that anywhere from 20-80% of children have residual OSAS post-operatively (4, 5). CPAP is typically the alternative therapy for OSAS, but adherence in children is limited, with up to a third dropping out, and the remainder wearing their equipment for only a portion of the night (8, 19, 20). Furthermore, young children with OSAS may develop midface hypoplasia from CPAP (21, 22). Thus, additional treatment options for childhood OSAS are desperately needed, with the realization that not all options will suit all patients. One such option may be NCS.

OSAS, inflammation, asthma/atopy and obesity: OSAS has been shown to be associated with inflammation in both children and adults (23, 24). For instance, C-reactive protein (CRP) is elevated in a dose-dependent manner in pediatric patients with OSAS (25, 26). Children with asthma have a high prevalence of OSAS, and children with OSAS are more likely to be asthmatic (27). Studies also suggest that children with atopy, as shown by

positive skin tests, are more likely to have histories suggestive of OSAS (28). Some studies of NCS have demonstrated residual OSAS (11, 13-16), as a result of which the American Academy of Pediatrics recommended that NCS should not be used as the primary treatment for moderate or severe OSAS. However, it is possible that specific subgroups of patients with moderate to severe OSAS, particularly atopic/asthmatic patients, may benefit more than others from NCS. This is further suggested by the large variability in patient response in some of the studies (15). It is possible that atopic patients are more NCS-responsive. Obese patients may also respond differently - possibly having a larger response as obesity is associated with inflammation, or conversely, a smaller response due to fixed structural narrowing from adipose tissue. No studies have specifically evaluated the response to NCS in atopic or obese subsets of children; or the effects of NCS on inflammation in children with OSAS; these will be assessed in the current study.

Genetic markers of NCS therapeutic response: The T_h2 subset of CD4-positive T cells are the primary defense of the body against helminth and other large parasite infections (29). Differentiation of T_h2 cells is promoted by various type-2 cytokines such as IL-4, IL-5, IL9 and IL-13. T_h2 cells also promote the development of allergic inflammation. IL-4 from T_h2 cells promotes the secretion of IgE antibodies from B cells, which then in turn promote the release of mediators of allergic inflammation, like histamine, from granulocytes such as mast cells and basophils (30, 31). IL-13 promotes asthma phenotypes like mucus production from goblets cells and hyper-responsiveness of airways (30, 31). Recently, a subtler role for T_h2 responses in asthma has become appreciated. It has been shown that asthmatics can be divided into at least two subsets, and one of the key differentiators between these subsets is the expression of T_h2 phenotypes in the lung (32). The authors of this study sought to quantify the effects of IL-13 in asthmatics, but the amount of IL-13 in bronchial brushings was below the level of detection. The investigators instead measured the expression of genes known to be induced by IL-13 in airways: periostin, CLCA1, and SERPINB2. ~50% of the asthmatics in the study had high expression of these 3 genes in airways, while the other 50% were indistinguishable from non-asthmatic controls with respect to expression of these genes. Asthmatics with the "T_h2-high" phenotype in their airways responded well to treatment with inhaled corticosteroids (fluticasone), while asthmatics with the "T_h2-low" phenotype largely did not respond to treatment. This demonstrates the utility of identifying distinct subsets of asthmatics before prescribing a treatment. Interestingly, a traditional marker of T_h2-dependent allergy, the number of allergens to which subjects developed a positive skin-prick-test, was not significantly different between T_h2-high and T_h2-low asthmatics, indicating that determining T_h2 status in the affected tissue for a particular condition is more relevant than general measures of overall T_h2 status. The effect of T_h2 status will be determined in the current study. In the future, this may lead to personalized treatment of the child with OSAS.

Side-effects of NCS: Although most patients tolerate topical corticosteroids without side-effects, adverse events including growth, endocrine and ocular dysfunction may occur. GlaxoSmithKline recently released information showing that children using their brand of NCS had a slowing of growth velocity of -0.27 (95% confidence interval [CI]: -0.48 to -0.06) cm over a year (clinicaltrials.gov # NCT00570492). However, it is not known how this information relates to children with OSAS, as OSAS itself can impact growth (33). In addition, the GlaxoSmithKline study used a dose of 110 mcg/nostril daily, which is double

the recommended pediatric dose that will be used in the current study. Another study of high dose nasal fluticasone showed no growth effects at one year (34). Suppression of the hypothalamic-pituitary-adrenal (HPA) axis has been demonstrated in children receiving inhaled glucocorticoids. Most studies have evaluated adrenal insufficiency in the setting of only inhaled glucocorticoids. However, in a study of subjects with asthma, 122 of 143 subjects were on combined inhaled and nasal steroids; 6.1% had a morning cortisol < 3 µg/dL (35). The combination of nasal steroids and inhaled steroids predicted dysfunction (as defined by a metyrapone test) of the HPA axis. Adrenal crisis is rare, but has been reported with higher dose inhaled steroids (36). Inhaled steroids have been associated with an increased prevalence of cataracts (37). The propensity of topical corticosteroids to cause side-effects depends upon the dose and potency of the steroid, extent of systemic absorption, use of other medications that may interfere with catabolism, and likely underlying genetics. Thus, specific studies on the prevalence of NCS side-effects in children with OSAS are needed to determine the risk of these sequelae in this particular population. This will be performed in the current study.

1.6 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, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). 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 efficacy of NCS *vs.* placebo in treating OSAS in children.

The primary objective of this study is to determine whether a 3-month course of NCS reduces the AHI in children with OSAS.

The secondary objectives are to:

- To determine which factors modify the response to NCS
- Determine the long-term effect of NCS vs. placebo in the treatment of OSAS in children
- Determine the side-effects associated with chronic NCS use in children with OSAS.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is a randomized, parallel, double-blind, placebo-controlled study with change in AHI as the primary endpoint. A screening sleep study will be performed in participants with clinically suspected OSAS (please refer to figure 1). Those who meet polysomnographic criteria will undergo a battery of baseline testing on a separate day. Participants with the following baseline results: (i) DXA scans showing spine or whole body bone mineral density < -2.0 standard deviations using race specific curves with adjustment for height Z-score, ((ii) ophthalmologic exam showing cataracts or intra-ocular pressure > 22 mm Hg on two measurements will be withdrawn from the study. All other participants will then be randomized in a 2:1 fashion to either NCS or placebo for 3 months.

3.1.1 Screening Phase

Children with OSAS will be recruited from the Sleep Center, as well as the Otolaryngology and Allergy Clinic at the Children's Hospital of Philadelphia. In addition, we will recruit from the Children's Hospital of Philadelphia primary care practices using real-time alerts in the electronic health record. This will be set up by the Pediatric Research Consortium (PeRC). Participants will be referred to the study team by their providers. The families who agree to be contacted will be called to discuss the study. Those who agree to participate in the study will be scheduled for a screening visit.

Parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study related procedures being performed.

At the end of this screening visit, a sleep study will be performed to confirm eligibility based on polysomnographic parameters.

3.1.2 Phase 1: Baseline visit & Randomization

Participants who met sleep study criteria will come back for a baseline visit that will include physical examination, cognitive and behavioral measures, knee height measurement, DXA scan (girls who are aged 10 or older and/or have attained menarche will have a urine pregnancy test before the DXA scan), phlebotomy (biomarkers, genetics, and cortisol levels), nasal swab for biomarkers and genetics, ophthalmology evaluation, OSAS symptoms questionnaires, nasal symptoms questionnaires, quality of life questionnaires and acoustic reflectance airway size measurement. Cognitive and behavioral measures will be obtained at a standardized time in the morning. The measurements of height and knee height will also be performed in the morning. Testing will be scheduled at the family's convenience, either all on one day or spread out over a few days. Participants with the following baseline results: (i) DXA scans showing spine or whole body bone mineral density < -2.0 standard deviations using race specific curves with adjustment for height Z-score, (ii) ophthalmologic exam showing cataracts or intra-ocular pressure > 22 mm Hg on two measurements will be withdrawn from the study and referred to clinical care. All other participants will then be randomized in a 2:1 fashion to either NCS or placebo for 3 months. Note that DXA results may not be available on the same day, in which case the participant

will be randomized, but will later be withdrawn from the study and referred for clinical care if the DXA results are abnormal.

3.1.3 Phase 2: 3-month visit

Participants randomized to both groups will receive monthly phone calls and come back at 3 months for a visit. Sleep study and all procedures performed at the baseline visit, except for physical examination, will be repeated at 3 months. Medication canisters will be weighed. Participants in the placebo group will then be referred to clinical care (for evaluation for further clinical treatment such as surgery if their sleep study is still abnormal, or for routine ongoing clinical surveillance if their sleep study has normalized). Children in the NCS group will be referred to clinical care if their sleep study shows severe OSAS or significant hypoxemia or hypercapnia, such that definitive treatment should not be delayed (AHI > 30/hr, more than 2% total sleep time with SpO2 <90%, end-tidal PCO2 > 60 mm Hg for > 5 minutes, or pathologic arrhythmias)(4). In addition, children with (i) DXA scans showing spine or whole body bone mineral density < -2.0 standard deviations using race specific curves with adjustment for height Z-score, (ii) ophthalmologic exam showing cataracts or intra-ocular pressure > 22 mm Hg on two measurements will be withdrawn from the study and referred to clinical care. Note that DXA results may not be available on the same day, in which case the participant will be randomized, but will later be withdrawn from the study and referred for clinical care if the DXA results are abnormal.

3.1.4 Follow-up Phase

In order to determine the duration of action of NCS therapy for OSAS, children in the NCS group who did not require referral to clinical care as detailed in 3.1.2 will be further randomized to either placebo or continuation of NCS. Half of the initial NCS group will continue treatment with NCS, and the other half will be switched to placebo.

This follow-up phase will continue for 9 months. Families will be called every month to check on symptoms and side effects. In addition, participants will come at 6 and 9 months for short visits during which symptoms and medical history will be reviewed, vital signs assessed, height and weight measured, side-effects assessed and medication canisters weighed. At 12 months, participants will come back for a visit that will include a sleep study and all procedures performed at the 3 month visit. Children with persistent OSAS abnormalities and those with abnormal DXA scans, abnormal hormonal levels or ophthalmologic exam will be referred to clinical care.

3.2 Allocation to Treatment Groups and Blinding

Randomization: A blocked randomization scheme (with block sizes that vary randomly between 2 and 4) will be employed to initially randomize subjects to NCS or placebo at baseline; the same approach will then be employed for the re-randomization at 3 months, when the subjects who were initially randomized to receive NCS will be re-randomized in equal numbers to receive NCS or placebo. The randomization will be stratified according to atopy/asthma, current use of inhaled corticosteroids for asthma (yes/no), obesity status and seasonality (spring/summer *vs* autumn/winter). Programs will be written in Stata to conduct the randomization, and the assignments will be stored in sealed envelopes stored in a locked cabinet that is only accessible to CTSA staff who are not affiliated with other aspects of the

study.

Blinding: The study will be double-blinded. All subjects, their families, investigators and study team members will be blinded, except for one research coordinator. In order to avoid bias and equipoise shifting, two research coordinators will be part of this study. One of them will be responsible for enrolling subjects and will be blinded to the treatment allocation status. The other research coordinator will be responsible for breaking the blind at the 3 month visit. She will refer participants allocated to placebo to clinical care, and communicate with the statistician regarding the randomization of participants initially allocated to NCS. Other investigators will evaluate research data (e.g., read polysomnograms) that are deidentified and coded to prevent becoming unblinded. Note that there is no physical exam after the baseline study. The statistician will generate a list of random numbers for study arm assignment, and a CTSA staff member who is not otherwise involved in the study will provide the drug/placebo.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per subject will be up to 15 months total including 12 months since randomization. The extra days are to account for interpretation of the sleep study and scheduling of subjects, including potential cancellations due to family circumstances. Of note, subjects initially randomized to placebo will be in the study for 3 months following randomization.

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

The study will be conducted only at CHOP. It is expected that 318 children will be recruited to produce 159 evaluable subjects 3 months after randomization, and 100 at 12 months.

3.4 Study Population

3.4.1 Inclusion Criteria

1) Age 5-12 years of age.

2) Mild to moderate OSAS, defined as an obstructive apnea index (AI) of 1-20/hr of total sleep time (TST) or obstructive hypopnea apnea index (AHI) 2-30/hr of total sleep time (TST).

3) Parent-related symptoms of habitual snoring (>3 nights per week)

4) No history of adenotonsillectomy or prior NCS use.

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

3.4.2 Exclusion Criteria

1) Severe OSAS or significant hypoxemia or hypercapnia on PSG, such that definitive treatment should not be delayed (AHI > 30/hr, more than 2% total sleep time with SpO2 <90%, end-tidal PCO2 > 60 mm Hg for > 5 minutes, pathologic arrhythmias)(4).

2) History of recurrent throat infections (as defined by the American Academy of Otolaryngology-Head and Neck Surgery Clinical Practice Guidelines For Tonsillectomy (7)) in the past few years as follows: > 7 episodes in the past year or > 5 episodes/year over the past 2 years or > 3 episodes/year over the past 3 years.

3) Abnormalities on baseline safety screening tests, i.e., DXA scan showing spine or whole body bone mineral density < -2.0 standard deviations using race specific curves with adjustment for height Z-score; (subjects may be randomized in the absence of DXA results; once the DXA results become available, subjects with abnormal results will be withdrawn from the study and referred for clinical care) or ophthalmologic exam demonstrating cataracts (except those with < 2 mm anterior polar cataracts), aphakia or other ocular abnormalities such as glaucoma, retinal coloboma, intraocular inflammation or microphthalmia.

4) Failure to thrive (weight/height < 5th percentile for age and gender), as this may be secondary to OSAS.

5) Severe obesity (BMI z-score > 3) as OSAS is likely to persist in these subjects.

6) Previous adenoidectomy unless adenoidal tissue has been documented to have regrown.

7) Previous adenotonsillectomy.

8) CPAP therapy.

9) Any NCS use in the past 3 months or NCS use for > 2 weeks in the past year.

10) Current immunotherapy or daily antihistamine use.

11) Recent (past month) nasal septum ulcers, surgery or trauma.

12) Other major illness other than asthma, such as craniofacial anomalies, endocrine or neuromuscular disease, or past history of cancer. This includes children with conditions that may be worsened by OSAS, such as hypertension or diabetes.

13) Current use of ketoconazole or other potent CYP3A4 inhibitors.

14) Families planning to move out of the area within the year.

15) Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.

16) Pregnancy.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures. Note that DXA results may not be available on the same day, in which case the participant will be randomized, but will later be withdrawn from the study and referred for clinical care if the DXA results are abnormal.

4 STUDY PROCEDURES

4.1 Screening Visit

- Informed Consent
- Medical Record Review
- Sleep study. Of note, participants who have undergone a recent sleep study (past 3 months) will not require a new one.

4.2 Study Treatment Phase

4.2.1 Visit 1: Baseline & Randomization

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- History and Physical Exam
- Vital Signs
- Cognitive and behavioral measures
- Knee height measurement,
- DXA scan (immediately preceded by pregnancy test when indicated)
- Phlebotomy (biomarkers, genetics, and cortisol levels)
- Nasal swab (biomarkers, genetics)
- Ophthalmology evaluation
- OSAS symptoms questionnaires
- Nasal symptoms questionnaires
- Quality of life questionnaires
- Airway size measurement
- Spirometry

- Percutaneous skin allergy test
- Randomization
- Dispensation of NCS or placebo

4.3 Phase 2 of the Study

Participants randomized to both groups will receive monthly phone calls, keep an infection log, and come back at 3 months for a visit.

4.3.1 Visit 2

Detailed description of study visit including all procedures – listed like above examples.

- Sleep study
- Vital Signs
- Cognitive and behavioral measures
- Knee height measurement,
- DXA scan (immediately preceded by pregnancy test when indicated)
- Phlebotomy (biomarkers, genetics, and cortisol levels)
- Nasal swab (biomarkers, genetics)
- Ophthalmology evaluation
- OSAS symptoms questionnaires
- Nasal symptoms questionnaires
- Quality of life questionnaires
- Airway size measurement
- Weigh medication canister
- Participants in placebo group will end their participation in the study at the end of visit 2. They will be referred to clinical care
- Re-randomization of participants in NCS group
- Dispensation of NCS or placebo

4.4 Follow-up Phase (only if applicable)

Children in the NCS group who did not require referral to clinical care as detailed in 3.1.2 will be further randomized to either placebo or continuation of NCS. Half of the initial NCS group will continue treatment with NCS, and the other half will be switched to placebo. Participants re-randomized to both groups will receive monthly phone calls, keep an infection log

4.4.1 Visits 3 & 4

Will be scheduled at 3 and 6 months respectively after second randomization to help with retention.

- Interim medical history
- Vital Signs
- Weigh medication canister
- OSAS symptoms questionnaires and nasal symptoms questionnaire

4.4.2 Visit 5: End of Study

Detailed description of study visit including all procedures – listed like above examples.

- Sleep study
- Physical Exam
- Cognitive and behavioral measures
- Vital Signs
- Laboratory tests
- Knee height measurement,
- DXA scan (immediately preceded by pregnancy test when indicated), blood work (biomarkers, genetics, and cortisol levels), ophthalmology evaluation,
- OSAS symptoms questionnaires
- Nasal symptoms questionnaires
- Quality of life questionnaires
- Airway size measurement
- Weigh medication canister

- Participants in both groups with persistent polysomnographic abnormalities are referred to clinical care.

4.5 Unscheduled Visits

In the rare circumstance where a patient requires an unscheduled visit for a true emergency, they will be seen in the Emergency Department. For minor issues, they will be seen by a member of the investigative team in a clinically appropriate time frame.

4.6 Concomitant Medication

All prior and concomitant medications used within 3 months prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.7 Rescue Medication Administration

N/A

4.8 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, or AEs. The Investigator 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.

4.8.1 Early Termination Study Visit

Subjects who withdraw from the study will have all procedures enumerated for Visit 5 at the early termination visit.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).

- Date of birth
- Zip code
- Race and ethnicity

- Medical history
- Surgical history
- Height and weight
- Medications history

Sleep study if performed in the last 3 months

5.1.2 History and Physical Examination

A structured history and examination will include:

- Asthma presence and severity
- Atopy
- Eczema
- Rhinitis
- Symptoms of OSAS
- Examination of the nares
- Clinical tonsillar size (0 - 4+)
- Visual oral airway patency using the modified Mallampati scale
- Standing height will be measured with a stadiometer (Holtain, Crymych, UK)
- Weight will be measured on a calibrated digital electronic scale
- Body mass index z-scores will be calculated

- **Ocular health:** Ophthalmologic exam including standardized measurement of recognition acuity, slit lamp examination to detect cataract, intraocular pressure measurement using i-Care tonometry, and a dilated fundus examination, performed by the CHPS Ophthalmology Core.

5.1.3 Vital Signs

Pulse and BP will be measured after the subject has been seated quietly for 10 minutes. For BP, systolic and diastolic BP will be measured once, using automated equipment, according to standardized guidelines. Cuff size will be determined by measuring the circumference of the upper arm, measured at the midpoint, and identifying the appropriate bladder size from a standard chart.

5.1.4 Laboratory Evaluations

Blood sampling will be performed for the following laboratory evaluations

- Systemic Biomarkers

5.1.4.1 Systemic Biomarkers

Systemic markers of atopy (serum IL-4 and IL-13) and systemic (serum TNFα and hsCRP) inflammation in response to NCS will be measured at baseline and 3 months from blood.

IL-4, IL-13 and TNFα will be measured using a multiplex kit manufactured by Meso Scale Discovery (Rockville, MD) on an MSD Sector 6000 Imager. MSD assays are well known for its wide dynamic range and high signal-to-noise ratios(38).

High sensitivity C-reactive protein (hsCRP) will be measured using a laser-based immunonephelometric method on the BNII (Siemens Healthcare Diagnostics, Deerfield, IL). Limits of detection for hsCRP are 0.16 mg/L, while total imprecision for hsCRP assays range from 2.1-5.7%.

5 mL of blood total will be required to run these tests. Samples will be drawn by pediatric CHPS nurses and will be labeled using participants study ID numbers. Tests will be performed in the CHPS Center for Human Phenomic Science (CHPS).

5.1.4.2 Urine pregnancy test

Female participants ages 10 and older or those who have attained menarche will be asked to provide a urine sample for pregnancy testing prior to the whole body DXA scan. Positive pregnancy results will be shared with the subject and not with the parent(s). Subjects will be encouraged to share the results with their parent (s). If desired by the subject, the CHOP pulmonary social worker will be consulted. Pregnant females will be excluded from the study.

5.1.5 Other Evaluations, Measures

- **Baseline Polysomnography:**

Overnight polysomnography will be performed in the 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 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: (39)

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

- **Neurocognitive and Behavioral measures** (the neurocognitive measures in non-English/Spanish speaking participants will be omitted unless a validated interpreted version is commercially available.):

    - The Epworth Sleepiness Scale modified for children
    - The Child Behavior Checklist (CBCL)(40)
    - Behavior Rating Inventory of Executive Function (BRIEF)
    - Conners Abbreviated Symptom Questionnaire
    - Conners Kiddie Continuous Performance Test Version 5 (K-CPT) for children aged 5 years and the Conners Continuous Performance Test (CPT-II) for children older than 5 years.Purdue Pegboard, a widely used test of fine motor coordination

- **Airway size measurement:**

    - Airway size will be measured using acoustic reflectance (Eccovision, Hollywood, FL), a noninvasive clinical technique which has been used successfully in children in order to measure both the nasopharyngeal and oropharyngeal airway diameter. This device has been used previously for research protocols (IRB #9752) and has been approved by the device committee. The participant wears nose clips and breathes into a mouthpiece for a few minutes.

- **OSAS symptoms:**

    - The Pediatric Sleep Questionnaire (PSQ) will be used

- **Nasal symptoms will be measured by the following questionnaires:**

    - Nasal Obstruction Symptom Evaluation (NOSE) scale, a validated scale of nasal obstructive symptoms (41), modified by deleting the question about sleep and written in child-friendly language.

- **Quality of life** (the Quality of Life measures in non-English/Spanish speaking participants will be omitted unless a validated interpreted version is commercially available:
    - Pediatric Quality of Life Inventory (PedsQL), a well-validated, generic measure of global quality of life
    - The OSAS-18 will be used as a disease-specific pediatric quality of life measure (42, 43).
    - Paediatric Rhinoconjunctivitis Quality of Life Questionnaire, a validated measure of rhinitis-specific quality of life.

Spirometry: Standard spirometry will be performed.

- **Allergy testing:** Percutaneous skin testing will be performed on the forearm with a bifurcated needle (Allergy Labs of Ohio, Columbus, Ohio) by pricking through a drop of the extract, which is then absorbed. The allergens will be commercial extracts (Greer Laboratories, Lenoir, NC)representative of local allergens in the greater Philadelphia area (44), including *Der P, Der F* (dust mite), *Fel d I (*cat), C*an f1*(dog), *Acer* (maple)*, Quercus* (Oak)*, Betula (Birch),* Poaceae (grass), *Ambrosia* (ragweed), and *Rumex* (dock sorrel). Reactions will be recorded by measuring the largest diameter of the wheal-and-flare response in millimeters at 15 minutes. The test result will be considered positive if the wheal is 3 mm larger than that elicited by the negative control.

- **Nasal Biomarkers:** Nasal markers of atopy (nasal IL-4 and IL-13) and local (fractional exhaled nitric oxide [FeNO], nasal TNFα) inflammation in response to NCS will be measured at baseline and 3 months from a nasal swab. Samples will be labeled using the participants study ID number and tests will be performed in the CHPS Center for Human Phenomic Science (CHPS), except for FeNO that will per performed in the Pulmonary Core Lab.

    - IL-4, IL-13 and TNFα will be measured using a multiplex kit manufactured by Meso Scale Discovery (Rockville, MD) on an MSD Sector 6000 Imager. MSD assays are well known for measuring cytokines from nasal secretion using a multiplex immunoassay.
    - FeNO will be measured with a portable device (NIOX MINO, Aerocrine, Morrisville, NC) that has been validated against chemiluminescence (45).

- **Genetic markers:** Whole genome expression profiles from upper airway cells to identify individuals with a T_h2-high phenotype will be generated. RNA will be extracted from nasal brushings and assayed on Illumina's HumanHT-12 v4 Expression BeadChip which contains over 47,000 probes derived from the National Center for Biotechnology Information Reference Sequence (NCBI) RefSeq Release 38. Following data normalization and summarization using Robust Multi-Array Average expression measures (RMA) samples will be grouped by T_h2 status using cluster analysis of IL-13 induced genes as previously described (32). Samples will be labeled using the participants study ID number and will be performed in the Center for Applied Genomics by co-investigator Dr. Hakonarson.

- **Growth:** Knee height assessment for short-term growth evaluation will be obtained using a high precision (0.01 mm) knee height measuring device (Marine Computer Tech Inc., Chadds Ford, PA) that measures lower leg length from the heel to the superior surface of the knee (46). This highly accurate device is able to detect significant growth of the lower leg in 6-8 weeks. This will be performed in the CHPS Nutrition Core.

- **Bone health:** Dual Energy X-ray Absorptiometry (DXA) is the most commonly used technique for clinical diagnosis of low bone mass in children. Female participants ages 10 and older or those who have attained menarche will be asked to provide a urine sample for pregnancy testing prior to the whole body DXA scan. Pregnant females will be excluded. Bone mineral density of the lumbar spine and whole body are the recommended measurement sites for bone density assessment in children (47). They will be assessed using a Hologic Discovery bone densitometer (Hologic, Bedford, MA) operating in Apex software version 3.3. The *in vitro* coefficient of variation is < 1% and the *in vivo* coefficient in children is < 2%. This will be performed in the CHPS Nutrition Core.

- **Adrenal suppression:**

    - Morning cortisol: Assays will be measured by a solid-phase, two-site sequential chemiluminescent immunometric assay run on an automated Siemens Immulite 1000 clinical analyzer according to the manufacture's specifications.
    - Adrenocorticotropic hormone: Assays will be measured by a solid-phase, two-site sequential chemiluminescent immunometric assay run on an automated Siemens Immulite 1000 clinical analyzer according to the manufacture's specifications. Blood will be collected into iced EDTA tubes and centrifuged at 4^{o} C.
    - DHEAS

- **Infection:** Families will keep a log of all infections and illnesses.

5.2 Efficacy Evaluations

5.2.1 Diagnostic Tests, Scales, Measures, etc.

The **primary objective** of this study, the change in AHI 3 months after randomization, will be measured by baseline polysomnography.

The following measures will be used to determine which factors modify the response to NCS and the side-effects associated with chronic NCS use in children with OSAS of this study 3 months after randomization:

- Cognitive and behavioral measures
- Knee height measurement,
- DXA scan
- Blood work (biomarkers, genetics, cortisol, DHEAS and ACTH)
- Ophthalmology evaluation

- OSAS symptoms questionnaires
- Nasal symptoms questionnaires
- Quality of life questionnaires
- Airway size measurement
- Spirometry
- Percutaneous skin allergy test

These measurements will be performed at the CHPS.

The following measures will be used to determine which factors modify the response to NCS, the side-effects associated with chronic NCS use in children with OSAS of this study, and the long-term effect of NCS vs. placebo in the treatment of OSAS in children 12 months after randomization:

- Sleep study
- Knee height measurement
- DXA scan
- Blood work (biomarkers, genetics, and cortisol, DHEAS, ACTH levels),
- Ophthalmology evaluation
- OSAS symptoms questionnaires
- Nasal symptoms questionnaires
- Quality of life questionnaires
- Airway size measurement
- Cognitive and behavioral measures
- Spirometry
- Percutaneous skin allergy test

These measurements will be performed in the CHPS.

5.3 Pharmacokinetic Evaluation

N/A

5.4 Safety Evaluation

Subject safety will be monitored by adverse events, vital signs, physical examinations (ocular health), sleep study results, laboratory data (cortisol, DHEAS, ACTH), cognitive and behavioral measures, and DXA scan results.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint is the change in AHI at the 3-month visit.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- The change in AHI at the 3-month visit in each group according to the presence of atopy or obesity.
- The change in AHI at the 12-month visit in each group
- The change in knee height, bone health, adrenal suppression, ocular health and infection at 12 months.

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

6.3.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects randomized at Visit 1.

The primary efficacy endpoint will be the change in AHI between Randomization and Visit 2.

Secondary endpoints will include the change in AHI at the 12-month visit in each group and the change in knee height, bone health, adrenal suppression, ocular health and infection at 12 months.

6.3.3 Pharmacokinetic Analysis

N/A

6.3.4 Safety Analysis

All subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.4 Sample Size and Power

Sample size for primary endpoint:

All sample size calculations were conducted using nQuery Advisor software. It is assumed that 50% of subjects will fail the baseline screening PSG. Thus, 318 subjects will be recruited initially. 159 eligible subjects will be randomized in a 2:1 fashion to NCS *vs* placebo, respectively; the initial group sizes will therefore be 106 NCS *vs* 53 placebo subjects. The 2:1 randomization ratio is to allow for further randomization for Aim 3. Based on our past studies (see *Preliminary Data)*, we will assume a drop-out rate of 5% at 3-months. Therefore, the available sample size for the primary endpoint analysis will be 100 NCS *vs* 50 placebo subjects. This is powered on a comparison of mean changes in AHI between NCS *vs* control subjects at 3-months, based on two prior studies (13, 15). The effect-size for the difference in mean changes between treatment groups for the Brouillette study, calculated as the absolute value of the difference in group means, divided by the pooled estimate of the SD of changes, was 0.87 (15), and for the Kheirandish-Gozal study was 1.75.(13) A two group t-test with a 0.050 two-sided significance level will have $\geq$ 99% power to detect the effect size of 0.865 (observed in (13)) when the sample sizes in the two groups are 100 and 50, respectively. In addition, the two group t-test will also have >99% power to detect the effect size of 1.75 that was observed in (15). We will therefore have excellent power to determine treatment group differences of the magnitude observed by these past studies. However, as the effect sizes were so different for these two studies, and as the current study will include a more heterogeneous population, e.g., children with more severe OSAS, the observed effect-size may be smaller. If so, we will have 81% power to detect an effect size of 0.50. An effect-size of 0.50 corresponds to a mean reduction in AHI of 4.2/hr in the NCS group and no change in the placebo group, assuming the SD of changes is 8.4 (as observed in (13)); and an AHI reduction of 1/hr with NCS (and no change in placebo) if the SD of change is 2 as observed in (15). Any smaller difference between groups with respect to changes in AHI would not be clinically meaningful. We are therefore well-powered to detect meaningful changes for the primary endpoint.

Sample size for secondary endpoints:

Comparison of the changes in AHI between treatment groups, according to whether or not subjects are atopic or obese: Based on preliminary data from CHAT (4), the proportion of children with asthma/atopy is expected to be ~31% while the proportion who are obese is expected to be ~34%. With 100 *vs.* 50 subjects in the NCS and placebo groups, respectively, the number of subjects in each subgroup is expected to be: 31 atopy/NCS, 69 non-atopic/NCS, 15 atopic/placebo, and 35 non-atopic /placebo. The power to test for an interaction was evaluated by constructing a contrast for a one-way comparison of means in nQuery, to test the hypothesis that the difference in mean reduction in AHI between subjects treated with NCS *vs* placebo is equal for subjects with *vs* without atopy. When the total sample size is 150, a 0.050 level two-sided t-test of the specified contrast for an interaction of atopy by treatment in a one-way analysis of variance will have 80% power to detect an effect-size of 0.51 (here the effect-size is calculated as the absolute value of the contrast

mean divided by the within group SD and scale; it represents an index of the size of the contrast). An effect size of 0.51 would be observed if the mean change (post minus pre) in AHI is -6/hr for atopic subjects *vs* -3/hr for non-atopic subjects in the NCS groups, when the changes in AHI are 0/hr for atopic subjects and non-atopic subjects in the placebo group; this also assumes that the SD of changes is 2.8; a simulation program written in Stata based on 10,000 simulated data sets also indicated that we have 80% power to detect a significant treatment group by atopic interaction for this scenario. If similar results are observed for assessment of obesity (mean change in AHI of -6/hr for non-obese subjects *vs* -3/hr for obese subjects in the NCS group, versus 0/hr for obese subjects and non-obese subjects in the placebo group) this will result in an effect-size of 0.503; this assumes that the SD of changes is 2.8 and 34% of children are obese, so that the number of subjects in each subgroup is 34 obese/NCS, 66 non-obese/NCS, 17 obese/placebo, and 33 non-obese/placebo. We will have 82% power to detect an effect size of 0.503. This degree of relative improvement in AHI for NCS *vs* placebo in the atopic *vs* non-atopic and in the obese *vs* non-obese groups is clinically meaningful.

Comparison of the changes in AHI at 12 months: For this endpoint, the 100 remaining NCS subjects (assuming there were ~6 dropouts) at 3-months will be re-randomized in equal numbers to continued NCS or placebo. Assuming a conservative drop-out rate of 10%, there will be 45 evaluable subjects per treatment group at 12 months. We anticipate that subjects treated with NCS will continue to improve (i.e., have continued reductions in AHI), while those on placebo will have a worsening of their condition (i.e., increases in AHI). We anticipate that subjects who continue on NCS will have similar (or greater) improvements during the additional 9 months of follow-up as were observed during the first 3 months of treatment. Assuming that NCS subjects have a mean reduction in AHI of 4/hr, while placebo subjects have a mean increase of 3/hr, a two-sample t-test will have 97% power to detect this difference, assuming that the common SD of changes is 8.4 (as in (15)); if the SD of changes is 2.0 (as in (13)), then we will have >99% power. However, if the observed differences of the current study are smaller, a sample size of 45 in each group will have 80% power to detect an effect size of 0.597; this would be observed if the mean reduction in AHI is 2.4/hr for subjects treated with NCS, *vs* no change for subjects treated with placebo, assuming a SD of 4.0(13).

Side effects of NCS: The proportion of subjects with side-effects will be computed (with 95% CI). The average number of side-effects (with 95% CI) will also be computed. We do not anticipate that there will be an appreciable number of side-effects in either treatment group, but we will have excellent power to detect a meaningful difference between groups. A Fisher's exact test with a 0.050 two-sided significance level will have 84% power to detect the difference between the 50 placebo *vs* 100 NCS subjects at 3 months, if 1% of placebo *vs* 15% of NCS subjects have side-effects at 3 months. For comparison of the 45 treated *vs* 45 placebo subjects during the second 9 months of follow-up, we will have 82% power to detect a difference between 1% *vs* 20% of subjects with side-effects, respectively. In addition, the proportion of the 100 subjects initially randomized to NCS who have side-effects at any time during follow-up will be computed (with 95% CI). An exact binomial test with a nominal 0.050 two-sided significance level will have 85% power to detect an adverse event rate of 6% amongst the 100 NCS subjects at any time during follow-up (*vs* a hypothesized rate of 1%).

6.5 Interim Analysis

There will not be an interim analysis as this study does not involve a life-threatening condition or a life-threatening outcome.

7 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

7.1 Study Drug Description

7.1.1 Packaging

Clinical supply description

For this study, the Investigational Drug Service (IDS) at the University of Pennsylvania will prepare blinded nasal spray bottles with a metered pump (to deliver 55 mcg/0.1 mL of fluticasone) with a 30 day supply of solution per bottle. The IDS will obtain the fluticasone from Hi-Tech Pharmacal. The IDS will purchase all supplies, gas-sterilize pumps/bottles, fill solutions under sterile conditions and dispense in 3-month increments labeled for individual study subjects.

7.1.2 Labeling

IDS will label the bottles of fluticasone and placebo. Both bottles will look identical.

7.1.3 Dosing

Fluticasone will be taken at bedtime. One squirt in each nostril will be administered by caregivers.

7.1.4 Treatment Compliance and Adherence

Compliance will be assesses by weighing medication canisters at each visit.

7.1.5 Drug Accountability

Adequate records of study drug receipt and disposition will be maintained by the Investigational Drug Service at Penn. Records of receipts, investigational drug orders, dispensing records, and disposition forms will be examined during the course of the study. The purpose of these records is to ensure regulatory authorities and the Sponsor that the drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the Investigator or designee and may not be used for any purpose other than that described in this protocol. At study completion, all drug supplies including partially used and empty containers must be returned to Sponsor or designee.

7.2 Placebo Description

7.2.1 Packaging

Clinical supply description

The IDS at the University of Pennsylvania will prepare blinded nasal spray bottles with a metered pump to deliver placebo/0.1 mL per pump, with a 30 day supply of solution per bottle. The bottle will be amber (same as the drug bottle). The placebo will contain the following:

- Bacteriostatic Saline (Sodium Chloride 0.9% with 0.1% Sodium Benzoate) 98.9%
- Polysorbate 20, NF 1%
- Geranyl Acetate 0.1%

The polysorbate and geranyl acetate are to prove the same floral smell as the fluticasone. Polysorbate 20, NF is a pharmaceutical grade emulsifier suitable for use in oral or topical solutions; it is used to solubilize insoluble oils into water. Geranyl Acetate is one of the natural components in rose petals that helps produce the natural 'scent' of a rose. Geranyl Acetate is a component in some chewing gums and candies, in proportions similar to or larger than what will be used in this solution. Additionally, the mixture will be passed through a sterilizing filter during preparation. The IDS will purchase all supplies, gas-sterilize pumps/bottles, fill solutions under sterile conditions and dispense in 3-month increments labeled for individual study subjects.

7.2.2 Labeling

IDS will label the bottles of fluticasone and placebo. Both bottles will look identical.

7.2.3 Dosing

Placebo will be taken at bedtime. One squirt in each nostril will be administered by caregivers.

7.2.4 Treatment Compliance and Adherence

Compliance will be assesses by weighing medication canisters at each visit.

7.2.5 Drug Accountability

Same as 7.1.5.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

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

8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be

summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 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.

8.4 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.

8.4.1 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.

8.5 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

8.5.1 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.

8.6 Investigator Reporting of a Serious Adverse Event to Sponsor

N/A

8.7 Medical Emergencies

Medical emergencies are very unlikely to occur in this minor increase over minimal risk study. The PI will be notified in the case of medical emergencies and participants will be referred to the nearest Emergency Department for clinical care.

STUDY ADMINISTRATION

8.8 Treatment Assignment Methods

8.8.1 Randomization

A blocked randomization scheme (with block sizes that vary randomly between 2 and 4) will be employed to initially randomize subjects to NCS or placebo at baseline; the same approach will then be employed for the re-randomization at 3 months, when the subjects

who were initially randomized to receive NCS will be re-randomized in equal numbers to receive NCS or placebo. An exception for this randomization schedule will be siblings. Specifically, siblings will be randomized to the same arm to avoid parental confusion with study drug administration. For example, parents may confuse study drug with placebo because both study drug and placebo look, taste and smell identical and parents may give the wrong medication to their children. The randomization will be stratified according to atopy/asthma, current use of inhaled corticosteroids for asthma (yes/no), obesity status and seasonality (spring/summer *vs* autumn/winter). Programs will be written in Stata to conduct the randomization, and the assignments will be stored in sealed envelopes stored in a locked cabinet that is only accessible to CTSA staff who are not affiliated with other aspects of the study.

8.8.2 Blinding

The study will be double-blinded. All subjects, their families, investigators and study team members will be blinded, except for one research coordinator as previously described. The statistician will generate a list of random numbers for study arm assignment, and a CTSA staff member who is not otherwise involved in the study will provide the drug/placebo.

8.8.3 Unblinding

An unblinded medical monitor *Dr. Sterni at Johns Hopkins University) will review any adverse events but the investigators will remain blinded.

8.9 Data Collection and Management

1. Confidentiality.

    - Data will be uploaded directly and stored in a password-protected file using the Research Electronic Data Capture (REDCap).

2. Security. A copy of the password-protected file will be stored on the PI's office computer, with the original in research secure server.

3. Anonymization. The identifiers will be destroyed after publication. The other data will be retained indefinitely.

8.10 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and the Investigator and other site personnel 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 the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

8.11 Regulatory and Ethical Considerations

8.11.1 Data and Safety Monitoring Plan

- The study will have an external Data Safety Monitoring Board (DSMB) and an external unblinded medical monitor.

- The role of the medical monitor will be similar to that used in the Childhood Adenotonsillectomy Trial (CHAT) trial.(4) The Medical Monitor (Dr. Laura Sterni, Johns Hopkins University) is a pediatric pulmonologist and sleep specialist. She will have access to unblinded data should the need arise for a "real time," clinically urgent decision regarding a subject's continued study participation. A class of outcomes will be established denoted as "Treatment Failures." This will be defined as a change in clinical status interpreted by the safety officer as requiring an immediate change to established clinical therapy for OSAS. Operationally, treatment failures will be identified by the research coordinator based on interim telephone calls and research visits, or contacts initiated by the subject. Information will be submitted to the safety officer who will make a final adjudication of the status of the subject. Data will be subsequently reviewed by the DSMB. The P.I. will make the final determination regarding withdrawing individual subjects. Note that as the study will utilize an intent to treat paradigm, every effort will be made to continue the subject in the study, regardless of whether the subject receives clinical treatment or not. Examples of treatment failures include worsening symptoms of OSAS such as sleepiness interfering with schoolwork, or development of complications associated with OSAS such as failure to thrive. Note that in the CHAT study there were only 9 of 464 (1.9%) children designated as treatment failures, so the numbers in the current study are expected to be low.

- The DSMB will be responsible for overall participants' safety during the study. The DSMB will be comprised of a pediatric pulmonologist, Sally L. Davidson Ward, MD; a neonatologist and sleep medicine expert, Robert Brouillette, MD; a pediatric otolaryngologist, David Tunkel, MD; and a biostatistician, Mekibib Altaye, PhD.

- DSMB members are experts in their field and are unrelated to this research.

- DSMB members do not have active or pending scientific collaborations with study investigators

- The DSMB will meet twice a year. The meetings will be held via teleconference.

- Once a month, the Medical Monitor and DSMB will receive reports of all adverse events

- On a quarterly basis, or more frequently if needed, summary reports of all AEs, SAEs, Urgent/Immediate Medical Referrals, and Treatment Failures by treatment arm also will be provided to the DSMB

- For each DSMB meeting, reports will be provided. These will include data on recruitment and baseline characteristics, pooled data on eligibility violations, completeness of follow-up and compliance, analyses of primary and secondary efficacy endpoints, subgroup and adjusted analyses, analyses of AEs and symptom severity, and analyses of laboratory data. 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

8.11.2 Risk Assessment

OSAS treatment delay in both groups: The potential consequences of untreated OSAS may include behavioral, cognitive, and physiological outcomes. The 3 month wait period in children randomized to placebo on visit 1 is below the range (up to 6 months) frequently encountered in clinical practices between diagnosis and treatment of OSAS, and therefore, it is not greater than minimal risk. The 9 month wait period in participants randomized to placebo on visit 2 is a slight increase above this 6 month range , but is low relative to the average, 3.3 years (range, 6 months to 13 years) that elapse between the onset of significant OSAS symptoms and surgical therapy. (48) Of note, participants randomized to watchful waiting in the CHAT study had a 7 month treatment delay without significant adverse events.(4) In any event, specific safeguards will be followed to ensure the participants safety. Regular monitoring for adverse events will also provide a mechanism for referring the child for evaluation for earlier treatment, if so recommended by the PI. Although abnormal DXA results are a withdrawal criterion, DXA results will not be available immediately. It typically takes many months to years for topical steroids to cause abnormalities in bone density.(49, 50) Thus, a delay of a few weeks is highly unlikely to result in harm.

Fluticasone treatment: Risks include slowing of growth velocity, suppression of the hypothalamic-pituitary-adrenal axis and cataracts among others. These risks are infrequent at the dosage used on this study and will be specifically studied in this protocol.

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 parent/guardian will stay overnight in the same room as the subject. The subjects may develop transient skin irritation as a result of adhesive tape.

Cognitive and Neurobehavioral 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.

Venipuncture: Venous sampling may cause a small bruise and occasionally result in fainting. The trauma of venipuncture will be minimized by applying a local topical anesthetic as needed to minimize discomfort. Venipuncture will be conducted by CTSA nursing staff who are skilled in working with children and by those who are familiar with Child Life Principles.

Blood pressure measurement: Blood pressure monitoring may cause some discomfort associated with cuff inflation.

Spirometry: Not greater than minimal risk. This is a standard clinical test with no side-effects. **Questionnaires**: Not greater than minimal risk.

Airway measurement: Not greater than minimal risk. There are no side-effects associated with this procedure.

DXA scan: Not greater than minimal risk. The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect participants.

Percutaneous skin allergy test: Not greater than minimal risk. This clinical test can cause mild discomfort.

Urine pregnancy test: providing a urine sample may be embarrassing. To mitigate this, the sample will be collected in a private location.

8.11.3 Potential Benefits of Trial Participation

Direct benefit: The effects of NCS in children with mild to moderate OSAS are unknown. Therefore, subjects may or may not benefit from participation in this study. Participants may benefit from identification of clinical problems, for instance hypertension that may require attention. If intranasal fluticasone is effective for the treatment of OSAS, participants on the fluticasone arm of the study will benefit from this treatment.

Indirect benefits: The results of this study will help us determine whether NCS are effective in the treatment of OSAS. This knowledge will be very valuable to society.

8.11.4 Risk-Benefit Assessment

The risks of this study are greater than minimal risk, primarily related to the risks associated with administration of the study drug

Although participating subjects may not obtain direct benefit, data from this study will help determine whether NCS are effective in the treatment of OSAS. This knowledge will be very valuable to society as this syndrome is frequent.

8.12 Recruitment Strategy

Participants will be recruited from the Sleep Center at the Children's Hospital of Philadelphia, and Allergy, ENT, and Primary Care offices. 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 Dr. Marcus or Dr. Tapia, they will be notified of this study by the physician they see in the clinic. 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 from ENT, Allergy and Primary Care offices. Also we will advertise the study using research recruitment tear pads that will be posted only in designated areas approved by CHOP Facilities Services. We will use the resources of The Recruitment Enhancement Core (REC) that provides assistance with recruitment plan development and may assist in identifying and contacting potential participants using the 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. Specifically the REC will send out emails to potential participants identified through the CRU. The email contains REC opt out language. Additionally, the REC will use the This Week at CHOP blast to promote the study. We will also promote the study on http://www.chop.edu/clinical-trials a public facing website that has been created to support Investigators at CHOP. All the Allergy and ENT providers will be informed of this study and referred to a study member if interested. Our team will coordinate the sleep study of these children.

8.13 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 used.

8.13.1 Waiver of Consent

N/A

8.13.2 Waiver of Assent

N/A

8.13.3 Waiver of HIPAA Authorization

N/A

8.14 Payment to Subjects/Families

8.14.1 Reimbursement for travel, parking and meals

The compensation details are below.

For subjects aged 8 years and younger, the compensation for participation will be given in trust to their parents as follows:

- The parent/caregiver accompanying the child to the sleep study will receive $100 cash for each sleep study (screening visit if not had a recent one, and visits 2 and 5) performed as a reimbursement for transportation, parking, meals, and baby-sitting costs for siblings.

- The parent/caregiver accompanying the child to daytime visits (1, 2, , and 5) will receive $100 cash as a reimbursement for transportation, parking, meals, and loss wages.

- The parent/caregiver accompanying the child to daytime visits (3 and 4) will receive $50 cash as compensation for time and effort.

For subjects aged 9 years and older:

- The parent/caregiver accompanying the child to the sleep study will receive $50 cash for each sleep study (screening visit if not had a recent one, and visits 2 and 5) performed as a reimbursement for transportation, parking, meals, and baby-sitting costs for siblings.

- The parent/caregiver accompanying the child to daytime visits (1, 2, and 5) will receive $50 cash as a reimbursement for transportation, parking, meals, and loss wages.

- The parent/caregiver accompanying the child to daytime visits (3 and 4) will receive $25 cash for daytime visits (3 and 4) as compensation for time and effort.

- Participants will receive $50 cash for each sleep study performed (screening visit if not had a recent one, and visits 2 and 5) as compensation for time and effort.

- Participants will receive $50 cash for daytime visits (1, 2, and 5) as compensation for time and effort.

- Participants will receive $25 cash for daytime visits (3 and 4) as compensation for time and effort.

8.14.2 Payments to parent for time and inconvenience (i.e. compensation)

Parents will not be paid for time and inconvenience.

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

As detailed in 8.14.1

8.14.4 Gifts

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

9 PUBLICATION

Data will be published in a peer-review journal.

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