Study Title: Pilot Study of a Self-Supporting Nasopharyngeal Airway in Hypotonia (ssNPA)

PI: David Zopf, MD

NCT#: NCT04846400

Protocol Approval Date: May 5, 2022

Appendices A-D, F-G, and N-S have been redacted by extraction for trade secret protection.

Pilot Study of Novel Nasopharyngeal Airway Device for Treating Upper Airway Obstruction in Pediatric Hypotonia

PROTOCOL NUMBER: HUM00189669

DATE: May 3rd 2022

VERSION: 1.4

INVESTIGATOR: David A. Zopf, MD

Investigator Signature Page

My signature below certifies that I have read and understand this protocol and agree to conduct the study in accordance with the specified protocol procedures and FDA's Good Clinical Practice requirements.

PRINCIPAL INVESTIGATOR NAME (Printed): Date:

PRINCIPAL INVESTIGATOR SIGNATURE: Date:

Table of Contents Page

1.0 BACKGROUND

1.1 Prior Clinical Experience and Rationale for Study

There is a critical need for safe, effective, and tolerable treatment options for highly prevalent, recalcitrant obstructive sleep apnea (OSA) in patients with Hypotonic Upper Airway Obstruction (HUAO). HUAO can occur in conditions such as cerebral palsy, hypoxic encephalopathy, and syndromic tone anomalies, such as seen in Trisomy 21. OSA is characterized by recurrent episodes of complete or partial upper airway obstruction during sleep, with associated sleep fragmentation and oxygen desaturations. In contrast to the 1-5% [1,2] frequency of OSA among children in general, children with hypotonia conditions have a significantly higher prevalence. In a study of patients with hypotonia who underwent polysomnography (PSG) for symptoms of OSA, all had OSA with 25% moderate and *56.3% severe* OSA [3]. Thus, not only are these patients likely to have OSA, but their OSA is likely severe, warranting tracheostomy. Despite the obvious upper airway collapse seen in most of these patients, there is a paucity of data in existing literature on prevalence and severity of OSA in these conditions; treatment efficacy, particularly with regards to multi-level obstruction; and duration of treatment efficacy.

The risks of untreated OSA include systemic and pulmonary hypertension, exacerbated neurocognitive deficits, hyperactivity with attention and focus issues, excessive daytime sleepiness, failure to thrive, endothelial dysfunction and inflammation, and insulin resistance [4-9]. In addition to airway obstruction at night, it is common for patients with HUAO to have labored breathing with airway obstruction, even while awake.

An attended, in-laboratory, nighttime PSG remains the gold standard for diagnosis of OSA; however, it does not provide information on the site of obstruction, or direct further therapies. The pathophysiology underlying upper airway collapse in hypotonic conditions is frequently multi-factorial and multi-site, with diffuse, poor muscle tone control. As such, traditional treatment modalities are frequently ineffective. The initial step in treatment of pediatric OSA in children with or without HUAO is considered to be adenotonsillectomy. Whereas adenotonsillectomy is curative in 36%-80% of otherwise healthy children with OSA [10], patients with hypotonia often have persistent severe OSA post-adenotonsillectomy, with minimal improvement in the severity of sleep apnea [3]. PAP delivered via nasal or full-face mask is a widely accepted therapy for persistent OSA particularly in older children, with only 50% or fewer adherent to therapy. However, children with HUAO, with manifestations of developmental delay and intellectual impairment, have significant challenges with PAP adherence [11,12]. In addition to poor adherence, PAP has significant drawbacks. Aerophagia, risk of aspiration either secondary to gastroesophageal reflux, or primary aspiration of oral secretions, may prompt concern for exacerbation of these comorbid conditions commonly seen in HUAO. Furthermore, risk of aspiration in conjunction with a patient's inability to remove a PAP mask themself poses a catastrophic potential.

Therefore, children with HUAO frequently require aggressive surgical treatments to relieve the obstruction. Tracheostomy, by bypassing upper airway obstruction, definitively treats upper airway obstruction, but at the cost of a highly invasive surgical intervention. Tracheostomy

introduces the need for home nursing and frequent care, and likely impacts the child's as well as the overall family unit's quality of life. Tracheostomy additionally has significant morbidity and rare but present mortality [13,14]. HUAO were responsible for 80% of tracheostomies performed for severe obstructive sleep apnea [14,15]. Patients with tracheostomy as a treatment for OSA have a significantly lower quality of life than other surgical modalities [16]. Therefore, some families may stay with palliative care. Palliative care means that the medical team understands the child is not breathing effectively, that this will not be treated, and that care will focus on keeping the child comfortable. **Providing patients with HUAO and severe OSA an effective non-surgical alternative would be transformative as these children would otherwise warrant consideration for tracheostomy or go on struggling to breathe**. Further, it may have a dramatic impact on health care costs associated with tracheostomy, care, and home nursing.

One of the current innovations to treat the challenges of pediatric patients with HUAO is a nasopharyngeal airway device (NPA). However, several limitations to current NPA devices necessitate a new and improved NPA device design that is effective, easy to use, and that demonstrates high adherence to effectively address the challenges of treating OSA in pediatric patients with HUAO. Treatment of OSA in HUAO presents an extremely difficult challenge due to diffuse multilevel obstruction with lack of muscular airway tone. This research is studying the use of a self-supported nasopharyngeal airway (ssNPA) device to learn about its tolerability and effectiveness as a treatment for OSA in patients with hypotonia.

2.0 PRODUCT DESCRIPTION

2.1 Intended Use

The ssNPA is intended to treat severe OSA in pediatric patients with HUAO. The device is a flexible, medical-grade silicone, tube-like device that is inserted into the patient's nasopharyngeal airway through one nostril, directly supporting the collapsed airway muscles and maintaining upper airway patency. The device is intended to be used by children with assistance from parents in a domestic setting as often as needed. The ssNPA is currently an investigational device and has been classified by the University of Michigan IRB as non-significant risk. Because of this, it has not yet been submitted to the FDA. In the future, we believe the ssNPA to be a class II device with indications for use in the treatment of obstructive sleep apnea (OSA).

2.2 Device Description

The current ssNPA device is made of a single piece of flexible, medical-grade silicone, as shown in **Figure 1**. It is inserted through one nostril and extends to the anatomic position bypassing the upper airway obstruction above the epiglottis. The ssNPA is a stand-alone and portable device that does not require any additional equipment or electricity. The ssNPA device has a soft and flexible silicone body which enables easy insertion. It contours to the airway passage while having sufficient material strength to support the collapsed muscles and allow for easy airflow.

[redacted]

[redacted]

[redacted] The device will be used nightly, and if it provides relief for the patient, may be used for daytime periods as well per the guidance of the study team. The device will be checked at least every 24hrs and changed if necessary. Patients will be sent home with multiple devices, all in sterile packaging.

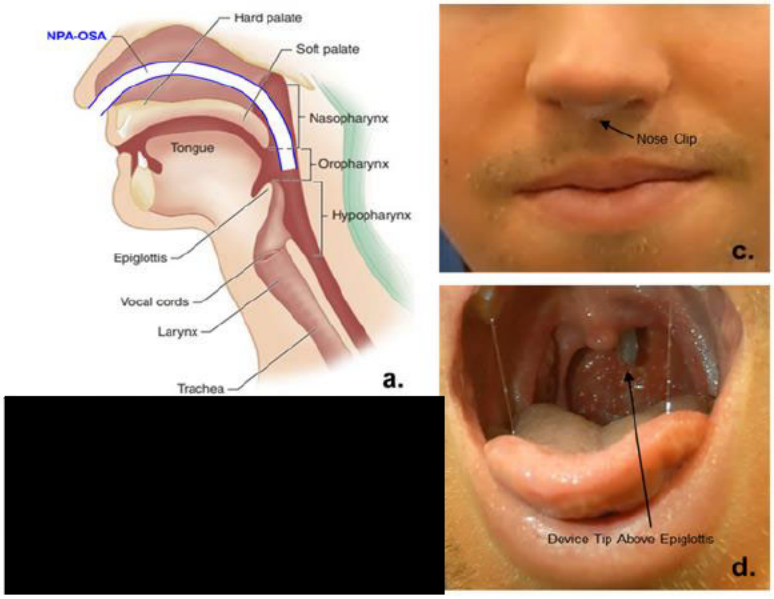


Figure 1: (a) Schematic view of ssNPA in proper position. The device spans from the entrance of the nose to just above the epiglottis, propping open the soft tissue in the upper airway (b) An image of the current ssNPA prototype with main components labeled. (c) Device in place with nose securement across nasal septum. (d) Device tip in proper position above epiglottis.

The design concept and material use of the ssNPA are the same as those of the nasal trumpet, which is commonly used by physicians/nurses for emergency care to be inserted into the nasal passageway to secure an open upper airway. This confirms the safety of using an airway device to support collapsed upper airway muscles and relieve obstruction.

RISK/BENEFIT ANALYSIS OF DEVICE

3.1 Comparison with Other Alternative Devices

PAP:

Positive airway pressure machines are the most common treatment for any kind of obstructive sleep apnea. They consist of a mask strapped to a patient's face which blows positive pressure into the airway to force any obstruction open. The primary concern with PAP machines is that they are extremely bulky and uncomfortable. Especially in pediatric patients, PAP adherence is very low because pediatric patients often remove the mask due to discomfort. In addition, there are risks of primary aspiration of oral secretions and secondary aspirations due to gastroesophageal reflux. This may prompt concern for exacerbation of these comorbid conditions commonly seen in HUAO. Furthermore, risk of aspiration in conjunction with a patient's inability to remove a PAP mask themself poses a catastrophic potential. In contrast to the discomfort and bulkiness of the PAP machine, the ssNPA is small, portable, and comfortable. It also does not carry an increased risk of aspiration when placed proximal to the glottis.

Nasal trumpet:

Nasal trumpets are used by physicians and nurses in a hospital setting. It is inserted into the nasal passageway to secure an open upper airway in the event of an emergency, such as a sudden airway obstruction. Nasal trumpets are only for short term use; they open up the airway initially so afterwards the patient can be ventilated or otherwise supported. They are not typically used as a treatment for OSA, but only has an emergency treatment for a temporary airway collapse. However, its similar mechanism of action makes it worth comparing to the ssNPA. Nasal trumpets must be administered by a health professional, such as a doctor or nurse, and cannot be done by the patient on themselves due to the required insertion technique and discomfort in placement. In contrast to the nasal trumpet, the ssNPA is for long term OSA treatment and is intended to be used by the patient or parent at home on a regular basis as enabled by its unique design.

Nastent:

Nastent™ is a single-use, over the counter nasopharyngeal airway product sold only in the UK and Japan. It also consists of a flexible silicone tube that is self-inserted into the nasopharyngeal airway to stent open the airway and allow for easier breathing. Nastent uses a tubular design, similar to a nasal trumpet, which when used for many hours can lead to clogging from mucus as well as a sore throat due to concentrated airflow only coming through the end of the tube. The ssNPA closely resembles the Nastent in that both are placed in the same anatomical position, both utilize a nose clip for device securement, and both are made of medical grade silicone. [redacted]

3.2 Minimization of Potential Risks with Device

Multiple measures have been taken to minimize the risks associated with the ssNPA.

Device fabrication

[redacted]

- **ssNPA Mold Fabrication:** [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- **ssNPA Rinsing, Packaging, and Sterilization:** The device will then be rinsed under clean water to ensure it is free from any debris, sealed in a Tyvek pouch, and sterilized by autoclaving for 50 minutes at 121 °C plus a drying period for 30 minutes.

Adverse event evaluation
The study team plans to regularly follow up with patients during the study to monitor them for any potential adverse events. They will do this by talking with patients' caregivers daily initially and less frequently as the study progresses via a phone call or video call. If the patient experiences any adverse events, as listed below, the PI will need to decide if this particular patient can continue the study to ensure optimal care.

Anticipated Adverse events:
- Skin irritation/allergy
- Bloody nose
- Difficulty breathing
- Necrosis
- Inflammation
- Persistent uncomfortable sensation (e.g. itch)
- Persistent gagging
- Airway foreign body or airway compromise (serious)
- Accidental dislodgment

These risks are being mitigated by the careful design and testing of the ssNPA. The ssNPA has been through over 45 design iterations to confirm optimal safety and comfort. Our manufacturing team maintains design control files for quality assurance. We have also done preliminary ex vivo biomechanical testing, described in Appendix C.

3.3 Potential Benefits of Device
All subjects who undergo polysomnography will learn whether or not they have OSA. Due to the design of this trial, all subjects will be offered ssNPA therapy. Therefore, all children who participate stand to benefit. In the R33 phase, those who are randomized to ssNPA will have their OSA treated immediately; those who are randomized to standard of care remain at the same risk as encountered during the course of typical clinical care. However, these latter children will be offered ssNPA therapy after an 8 week period, a time when they are still unlikely to have received interventions clinically due to waiting lists for surgery or PAP. What we learn from this study may significantly improve treatment of OSA in children with hypotonia.

The potential benefits for the investigational ssNPA device in this study include:
- An alternative to CPAP for non-compliant patients
- Ability to treat a wide range of OSA severities (unlike other CPAP alternative devices which are often targeted only for mild OSA)
- Non-surgical option, thus no surgical risk
- Reduced risk of aspiration from oral secretions
- Standalone
- Low profile
- Portable
- Comfortable
- Convenient

We believe that these benefits are significant and that with the collected evidence and testing thus far, the risks are much lower than the proposed benefits.

3.4 Previous Human Experience

The Principal Investigator (PI) of this proposal, Dr. David Zopf (UM Otolaryngology), has led a novel paradigm in using airway stenting with a nasopharyngeal airway (NPA) as a treatment for patients with hypotonia. One of the key clinical needs of current NPA devices for the treatment of UAO in a non-surgical manner is an improvised attachment [17,18,19]. The current attachment method in clinical practice is to use a safety pin pierced through to secure the endotracheal (ET) tube. Strings are attached to the safety pin and then to the cheeks of the patient using medical adhesive tape to prevent distal migration. The above procedure is performed by an Otolaryngologist in a clinical setting. Parents are trained and guided through the required maintenance, so the device can be maintained at home for a couple of weeks, a year, or even more. Implementation of the improvised attachment takes significant clinician time of at least an hour for placement and education. To maintain the NPA treatment, parents must suction secretions through the tube, clean the NPA device, and fabricate additional improvised attachment devices [20]. Often, the tape needs to be replaced when it loses its adhesive properties because the child has normal sweating, drooling, or nasal secretions. The continuous re-taping can weaken the stability of the NPA placement, resulting in skin tears and improper positioning of the ET tube. Moreover, the safety pin does not permit performance of magnetic resonance imaging (MRI) if needed. Although an NPA is shown to be safe and effective, very few patients currently receive the treatment due to the perceived decrease in quality-of-life for the child.

We have collaborated with the Michigan Institute for Clinical and Health Research (MICHR) to assess feasibility within clinical care of two pediatric patients with profound HUAO and severe OSA under the Innovative Care Consent process. [redacted]

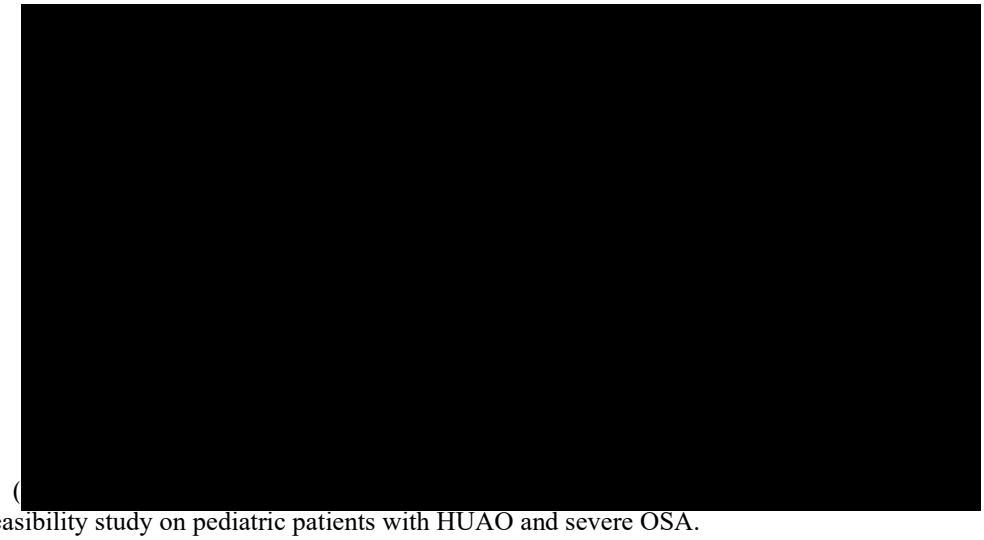


Figure 2: Feasibility study on pediatric patients with HUAO and severe OSA.

The first clinical care assessment was in a 9-year-old male with spastic, quadriplegic cerebral palsy, shunted hydrocephalus, seizure disorder, and very severe OSA. Upon presentation, he had labored breathing while awake with overt, upper airway obstruction. Endoscopic examination demonstrated diffuse, multilevel upper airway collapse, with complete collapse at the retropalatal and retrolingual areas. This patient had immediate relief of his airway obstruction after placement of the ssNPA and the mother reported it led to significant amelioration in symptoms of OSA with improvement in sleep continuity and daytime functioning. Baseline polysomnography (PSG) data of this patient demonstrated a total Apnea–Hypopnea Index (AHI) of 63.3 with associated oxygen desaturation to a nadir of 65%. The post PSG AHI after 12 months wearing the device reduced to 5.2 and the oxygen saturation nadir had improved to 85%. The second clinical care assessment was in a 17-year-old female with spastic, quadriplegic cerebral palsy, seizure disorder, and very severe OSA (baseline AHI of 94.5) with profound oxygen desaturation to 41%. Following placement of her ssNPA, she had complete resolution of her diffuse, extremely severe upper airway obstruction with a post PSG AHI of 0 and oxygen saturation nadir 87%.

These highly encouraging clinical treatments demonstrated the ssNPA's initial safety and ability to successfully treat severe OSA with minimal risk. However, this early version of ssNPA device required a trained Otolaryngologist for the placement in a process that would last at least an hour for device customization, placement, and education. Furthermore, to maintain the NPA treatment, parents must suction secretions through the tube, clean the NPA device, and fabricate additional improvised attachment devices using a safety pin through the ET tube and tape to hold the device in place across the patient's face. Often, the tape needs to be replaced when it loses its adhesive properties because the child has normal sweating, drooling, or nasal secretions. The continuous re-taping can weaken the stability of the NPA placement, resulting in skin tears and improper positioning of the ET tube. Moreover, the safety pin does not permit performance of magnetic resonance imaging (MRI) if needed. **Therefore, we anticipate that the new design of the ssNPA,**

as shown previously in Figure 1b, will not only show similar effectiveness in pediatric patients with HUAO, but that it will also prove easier to maintain and use for patients and their families.

Similar device studies
A recent study on the Nastent device has shown no complications [21]. In addition, a current clinical study of the Nastent sends users home with several sizes to try for 14 days and uses a home sleep test device to monitor sleep quality and snoring.

3.5 Justification for the Investigation
Because of the risks and inconsistencies present with current treatments for HUAO, there is a clear need for a safe and effective treatment for HUAO. By introducing a novel non-surgical method that has demonstrated initial clinical promise for some of the most severe, challenging cases of OSA, our hope is to provide an immediately translatable tool to improve critically important breathing and overall wellbeing of patients with hypotonic airway obstruction. ***Therefore, the goal of this proposal is to demonstrate efficacy of a new NPA device that is effective, easy to use and with high adherence to support long-term use and compliance.***

4.0 OBJECTIVES

4.1 Primary Objective R61 phase

1. Assess the tolerability, safety, comfort, ease of use, and ease of maintenance of the ssNPA in treating pediatric OSA

4.2 Secondary Objectives R61 phase

1. Confirm ssNPA device design
2. Evaluate changes in sleep quality, snoring, and daytime sleepiness
3. Optimize the ssNPA insertion protocol
4. Optimize the ssNPA sizing protocol
5. Optimize the surveys/questionnaires for use in the larger clinical study

4.3 Primary Objective R33 phase

1. Demonstrate device efficacy which is defined by 50% or greater reduction in AHI and reduction in AHI to <15/hr.

4.4 Secondary Objectives R33 phase

1. Improvement in caregiver noted night-to-night witnessed apnea and sleep disturbance
2. Adherence to device use
3. Quality of life improvement for both children and caregivers

5.0 STUDY OUTCOMES

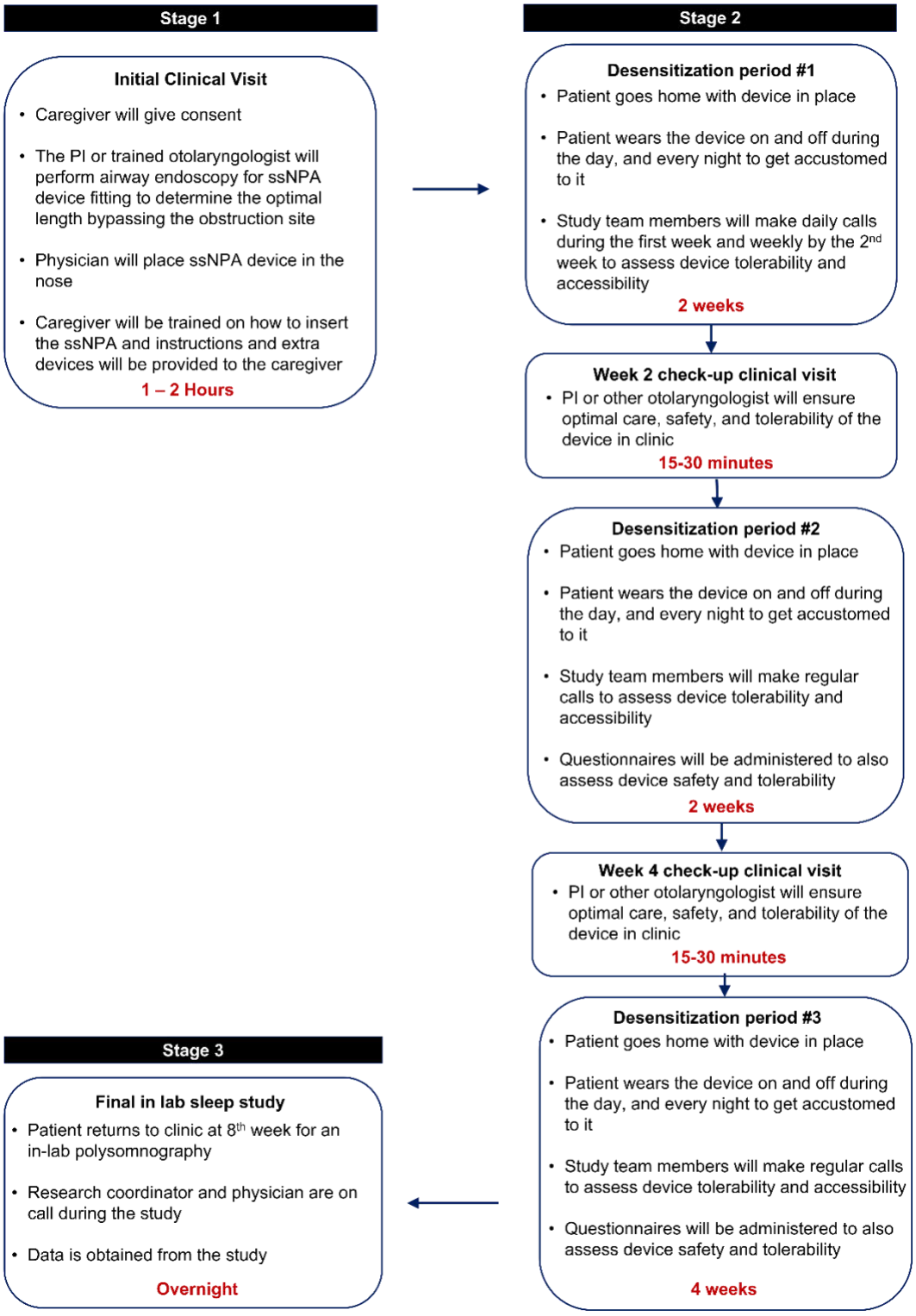
5.1 Safety/Tolerability Outcomes

Safety/tolerability outcomes will be assessed by 10-point and Likert scales measuring various milestones representing the acceptability of the device, including ease of use, tolerability and comfort. This will be addressed by the study debriefing via patient and/or parent interviews and questionnaires.

5.2 Efficacy Outcomes

We anticipate that use of the ssNPA will show clinically meaningful improvement (reduce the AHI by at least 50% and to a level <15) in substantial proportion of children with OSA and that the device will be able to be tolerated by greater than 60% of children and parents. Moreover, we expect that subjective sleep-related symptoms including impaired sleep quality, snoring, and daytime sleepiness, as well as quality of life for both parent and child will be improved. Exploratory analyses will determine changes in oxygen saturation nadir, sleep efficiency and possible improvement in sleep architecture such as increase in sleep efficiency, stage N3 and REM sleep. In addition, the insertion protocol will be optimized to make sure that it is safe, effective, and acceptable by parents/caregivers for ssNPA self-insertion. The current sizing protocol for physician will also be optimized to effectively help physicians to determine the proper length for ssNPA for each patient. These protocols will guide the larger clinical trial in R33 phase.

6.0 STUDY DESIGN



7.0 SUBJECT POPULATION

7.1 Inclusion Criteria

- Children with HUAO: This includes those who newly diagnosed with OSA. These children will undergo overnight polysomnography to determine the presence of OSA (AHI>10 or AHI>5 with nocturnal hypoxemia defined as SpO2 nadir <=75%). Those with an AHI>10 will be randomized to ssNPA therapy (R33 phase).
- Aged between 3-21 years old.
- Post adeonotonsillectomy or those with contraindications to tonsillectomy.
- Tonsil size 2+ or smaller.
- Parent/caregivers willing and able to provide informed consent and child willing and able
- to provide assent, where appropriate.

7.2 Exclusion Criteria

- AHI ≤10 on polysomnogram without hypoxemia.
- Any medical reason why ssNPA therapy may not be suitable
- Active COVID 19 infections
- ETCO2 or TCO2 values >60 mmHg for >10% of sleep time on PSG
- Psychiatric, medical, or social factors likely to invalidate assessments, make adherence with ssNPA highly unlikely or make local follow-up at 8 weeks unfeasible. Some psychiatric conditions may be provoked or exacerbated by OSA, and those most commonly implicated – Attention Deficit/Hyperactivity Disorder, Conduct Disorder, and Oppositional Defiant Disorder – will not be exclusions. However, more pervasive conditions such as severe autism will be excluded.
- Presence of supraglottic airway collapse or more distal airway stenosis or collapse (for example glottic, subglottic stenosis, or concern for distal airway stenosis or malacia)
- moderate/severe tracheobroncomalacia
- Need for anticoagulative therapy
- Bleeding disorder
- Restrictive thoracic disorders
- Silicone allergy

8.0 STUDY DURATION

Subject participation will be approximately 8 weeks long.

9.0 STUDY PROCEDURES

9.1 Recruitment and Screening

Patients will be recruited from Michigan Medicine clinics, including Dr. David Zopf's (PI of this project) Pediatric Otolaryngology Clinic, Physical Medicine and Rehabilitation (PM&R), or referred from UM Sleep Medicine Clinic. The patient lists provide the first line of screening for inclusion criteria and exclusion criteria.

Potential subject candidates will be informed about the proposed study before the study begins. If the patient's legal caregiver is interested in participating in the study, the study consent form will be emailed/mailed to them for their review prior to signing with a team member. We anticipate most pediatric patients will not be physically able to provide assent. The study team (including PI) will be responsible for answering any questions before the patient's caregiver consents to participate in the study.

9.1.1 Screening (+/- 30 days prior to enrollment)

The complete screening examination and subject histories will include, where medically possible:

- Demographics (date of birth, gender, ethnicity)
- Medical history
- Medication history (current prescription and chronically used non-prescription medications)
- Vital signs and physical assessment
- Clinical laboratory tests, including any sleep assessments

Any patients that do not meet study criteria, whether consent was obtained or not, will not be enrolled into the study. These patients will not be counted in the overall study enrollment numbers but will be listed on the screening log.

9.2 Study Assessments

Stage 1: Initial clinical assessment

After consent (and assent where appropriate) has been obtained, the PI or an otolaryngologist on the team, will perform an endoscopic measurement of the patient's airway to select the correct ssNPA length to bypass obstruction (a series of ssNPAs with pre-made lengths will be available). The ssNPA will be fully inserted through the nose by the Otolaryngologist and endoscopically checked to ensure adequate length bypassing obstruction and proper fit within the nose (see Appendix D for device sizing). Initial placement may be performed following topical nasal lidocaine/neosynephrine, which is commonly performed in routine flexible awake laryngoscopy. In our usability testing with patients and team members, brief mild discomfort can occur during initial placement, which resolves in seconds once the ssNPA is in place. In our observations, the brief initial discomfort improves with increased use, with acclimation of nasal environment.

Caregivers will be trained to perform the ssNPA insertion on the child in the clinic. In addition, they will be given an Instruction Brochure which provides information about OSA, demonstrates how to use the ssNPA, and provides information on the safety concerns of and proper care for the ssNPA device. The materials have been developed in concert with our tracheostomy team and are based on materials that provides similar robust care education. Families will be provided with a copy of the ssNPA desensitization protocol for the next 8-week (or less) desensitization home evaluation (see Appendices E-G for the caregiver documentation). We also will provide extra ssNPA devices to the patient so the device can be replaced bi-weekly.

Stage 2: 8-week home evaluation

After the first clinical assessment, the subject will be sent home with the ssNPA in place for home evaluation purposes for approximately 8 weeks, with two clinical in-person check-ins at weeks 2 and 4. As HUAO often results in obstructive events, both at night and while awake, we anticipate the ssNPA may be used for a large proportion of a 24-hour period in many children. The ssNPA desensitization protocol provides step-by-step instructions on how to help children get comfortable with placement of the device during daytime, after which, they will progress to use the ssNPA at night. Our team will work closely with parents/caregivers to follow instructions in the protocol to achieve adherence to ssNPA during these 8 weeks. The parent or guardian will be instructed how to insert the ssNPA and will be encouraged to have the child wear it for increasing intervals while awake to allow the child to acclimate to wearing it. This will also prepare them for wearing the device during the night. If the child feels comfortable with the ssNPA, it will be kept in place during the day as well. Feedback from families regarding desensitization during the R61 phase will optimize the desensitization protocol for the R33 phase.

Demonstration and instruction will be provided on cleaning and suctioning (Appendix F); the latter is required for any build-up of nasal secretion, particularly during respiratory illness. Indeed, during periods of respiratory illness, the ssNPA may provide relief for breathing disturbances, as has been observed in our pilot patients. Adherence will be followed and fostered by a registered nurse with extensive experience in desensitization among children in the Pediatric Sleep Clinic who require PAP. Customized ssNPA desensitization will be modeled on our experience with PAP desensitization. These efforts to promote adherence will match or exceed what we routinely provide to achieve a PAP adherence rate of 60-70% in children.

Families will return to the clinic at weeks 2 and 4 to ensure optimal care and evaluate the device safety, tolerability, and acceptability. In between the clinic visits, regular contact will be made with families by the team, daily during the first week and weekly by the 2nd week (see Appendices H-K). During these calls, caregivers will report night to night witnessed apneas, improvement in daytime awareness, improvement in sleeping patterns of the patient, and any adverse events. Beside the two clinical visits at 2nd and 4th week, the number and frequency of extra visits will depend on: (1) the child's current threshold; and (2) how the child and family advance through each step of the desensitization protocol. The decision to hold on a particular step of the desensitization program will be based on whether the child's current level of anxiety or opposition is elevated. A recommendation to discontinue ssNPA treatment may be made if the child or family do not make progress with wearing the device in 2-4 weeks (depending on the number of visits during that time). Discontinuation of ssNPA therapy may occur after case consultation with other members of the study team to ensure that all strategies have been considered.

Table 3. Milestones for successful completion of the R61 phase

R61 Milestones	Goal (out of 5 subjects)
1. Device optimization and manufacturing in clean/sterile manner	100%
2. Parent report of ease of insertion;>=5 on Likert scale of 1-10	60% (3 of 5)
3. Child able to tolerate device in place	60% (3 of 5)
4. Child able to maintain device in place during sleep	60% (3 of 5)
5. Parent report of adherence based on diary	60% (3 of 5)
6. Comfort rating>=6 on Likert scale of 1-10	60% (3 of 5)

Evaluation of the device safety, tolerability, and acceptability will be assessed by a survey of patients and caregivers using a validated questionnaire with 10-point response scale (Appendix K). Mean and standard deviation scores as well as the percentage of those reporting satisfactory or better will be assessed. Device safety will be determined by adverse events

evaluation (Appendix L). Any possibly-related adverse events (e.g. nasal skin necrosis or device displacement) will be evaluated through clinical visits and caregiver's feedback using standardized case report forms. Milestones for the R61 phase are detailed in Table 3. Likert scale scoring will be used to assess ease of insertion, tolerability while in place, ability to maintain the device in place while sleeping, and comfort level. Information will be obtained from parents/caregivers. In addition to the listed milestones, open response feedback will be obtained from families to determine if design changes are required specific to this population that may improve usability.

Stage 3: In lab sleep study

When the patient has fully acclimated to the device, at approximately 8 weeks, an in-lab PSG will be performed in the UM Sleep Disorders Laboratory in order to quantify the relief of obstruction (measured by AHI) while wearing the ssNPA. Sleep studies will include six EEG channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1 of the 10-20 international electrode placement system), 2 electro-oculogram channels (right and left outer canthi), chin and bilateral anterior tibialis surface EMG, 2 EKG leads, nasal and oral airflow (thermocouples), nasal pressure through pediatric sensor cannulae, thoracic and abdominal excursion (inductance plethysmography), and finger oximetry with pulse waveform. All recordings will be made on digital equipment (Compumedics, Inc.) with which the investigators have extensive laboratory-wide clinical and research experience. End-tidal or transcutaneous CO2 will be monitored per the AASM guidelines for pediatric PSG [22]. A research coordinator and a physician will be on call by page during the studies. Nocturnal PSGs will be scored by a single, experienced technologist masked to subject identity. Borderline polysomnographic features will be arbitrated between the technician and Dr. Fauziya Hassan, MD, pediatric sleep physician. Scoring for sleep stages, respiratory events, periodic leg movements, and arousals will follow standard criteria for children [22].

In addition, after the PSG results have been generated, a study team member will call the patient's parent or caregiver to inform them of the results. The parent or caregiver will then fill out a final questionnaire (10-point Final questionnaire; Appendix M) allowing them to share their perceptions of the device tolerability and acceptability. This questionnaire will be administered using a 10-point response scale and mean and standard deviation scores as well as the percentage of those reporting satisfactory or better will be assessed. During this assessment, open response feedback will also be obtained from families to determine if design changes are required specific to this population that may improve usability. In addition, at baseline and at the final visit, sleep questionnaires (including the Pediatric Sleep Questionnaire [23], OSA-18 [24] and the children's version of the Epworth Sleepiness Scale [25]) will be completed by caregivers along with the Pediatric Quality of Life instrument [26] and the Family Impact Questionnaire [27]. These items are anticipated to be utilized in the R33 phase and will be tested in the R61 phase to determine the level of subject burden.

9.3 Schedule of Events Table

	Screen	Day 0	Week 1-2	End of Week 2	Week 3-4	End of week 4	Weeks 5-8	At 8th week (approx)
Informed Consent		X						
Medical Hx/Medication Hx	X							X
Vital Signs/Physical Assessment	X							X
Clinical Laboratory Tests (eg polysomnography)	X							X
Baseline questionnaires		X						
Device placement		X						
Parent training		X						
At home device use			X		X		X	
Device tolerability surveys			X		X		X	X
Clinic visit				X		X		X
Adverse events evaluation (through daily/weekly phone calls)			X		X		X	X
Sleep and QofL surveys		X						X
Overnight sleep study								X

9.4 R33 Phase – Randomization

After the R61 phase is successfully completed, for the R33 phase we will recruit 40 children with HUAO meeting the inclusion criteria of severe OSA (AHI>10 or >5 with hypoxemia) with the additional requirement that all subjects require the presence of at least one symptom of OSA (such as snoring 3 or more nights per week, daytime sleepiness, or hyperactive/inattentive behaviors). These latter symptoms will identify children at the highest risk for OSA and will minimize false positive from the baseline PSG. The exclusion criteria are the same as those delineated in the R61 phase clinical study.

Recruitment will occur from all clinics as well as community sources. In order to ensure that sufficient children complete the protocol and we have enough data from 40 subjects for our data analysis, we may recruit up to a total of 50 subjects to include for those children who may drop out before the end of 8 weeks study. All children will undergo a baseline PSG to determine eligibility and establish baseline data. All families will complete a questionnaire battery at the time of baseline PSG to acquire baseline measures. Eligible patients will be randomized 1:1 to receive (1) immediate therapy with the ssNPA device or (2) standard of care (SoC). The study will be designed as a randomized wait-list controlled clinical trial such that all children stand to benefit. Randomization will be stratified by baseline AHI scores (AHI>30 vs. ≤30).

At 8 weeks the ssNPA group will be able to continue the ssNPA for an additional 8 weeks while the SoC group will be offered the ssNPA for 8 weeks. At the end of the 8 week period, all children will undergo an in-laboratory PSG and repeat the questionnaire battery.

9.4.1 Active group (ssNPA):
Children randomized to the ssNPA device will have a device length sized and fitted by an otolaryngologist as described in the R61 phase. Families will be instructed on use of the ssNPA and an experienced nurse will assist each family with our desensitization protocol. Briefly, this will include an overview of the ssNPA and have the child and parent handle the device. If no child anxiety the parent will be requested to insert the ssNPA. A timetable will be agreed upon with dates when to move to the next step. Parents will be taught how to clean the device and will be educated and provided with handouts regarding safety and hygiene concerns. Children will be encouraged to use the ssNPA for 8 weeks, at which time a PSG will occur for primary outcome assessment. During these 8 weeks, regular contact will be made with families by the team to make sure they are comfortable with using the device. We will make daily contact during the first week of using the device and will continue during following weeks if needed. We will also ask parents/caregivers to send us a photo of the child wearing the ssNPA before parents go to bed and also in the morning. A sleep diary will also need to be filled out every day during these 8 weeks to report the child sleep and wake up time. After the 8-week PSG, the active group will continue wearing the ssNPA for another 8 weeks and have the final PSG at Week 16. The families will complete several validated assessment tools same as the baseline visit for comparison of subjective endpoints at the end of each 8-week period. Subjects and families will be notified that consent to participate is voluntary and can be withdrawn at any time.

9.4.2 Waitlist Control Group; Standard of Care (SoC):
Children randomized to the SoC will be treated based on the usual clinic standard of care for the initial 8 weeks after randomization. During the waiting time, they will continue to receive the treatment they would have had before which will likely include being placed on the waiting list for PAP. In our institution it is common for it to be six months from initial referral to PAP titration and approximately 8-10 weeks from the time of a baseline study to a PAP titration. As such, it is unlikely that the waitlisted children would receive PAP therapy clinically before the end of the proposed trial. During the 8 weeks waiting time, the control group will also be contacted by phone to maintain a connection with the team to minimize the chance for them to drop out. As with the active group, a PSG will occur 8 weeks after randomization for primary outcome assessment. At

Week 8, SoC group patients will also be offered the ssNPA device, and those who opt to receive the device will be fitted with the device to start using it for the following 8 weeks. Those who decline the ssNPA will continue with usual clinical care. If indicated, tracheostomy will be discussed at initial clinic visit and if a family prefers this intervention, it will be offered. However, our experience is a large majority of patients would rather elect palliative care. During the 8 weeks, the study team will be in regular contact with families as detailed above to make sure they are comfortable with using the device. All SoC group participants will then have the final PSG at Week 16.

The families in both active and SoC groups will complete several validated assessment tools same as the baseline visit for comparison of subjective endpoints at both 8 and at 16 weeks. Subjects and their families will be notified that consent to participate is voluntary and can be withdrawn at any time.

9.5 TREATMENT INTERRUPTIONS-DISCONTINUATION CRITERIA

9.5.1 Treatment Interruption Criteria

In the event of patient illness, the patient will temporarily stop study treatment. Because nasal secretions and other upper respiratory symptoms can interfere with accurate data measurement and observation of treatment, the patient will have the option of pausing using the device until symptoms subside. Alternatively, if caregivers feel the device is providing symptomatic relief during the concurrent illness, they may continue use – however assessments, such as PSG will be postponed until resolution of acute illness to minimize artifact. Additionally, in the event of any temporary family emergency or necessary situation, the patient may also temporarily stop using the device. If for some reason there is a need for a different sized device, the treatment maybe paused while the new device is manufactured and delivered to the family. Observation will resume once the patient is treated with the new device.

The decision to hold on a particular step of the desensitization program will be based on whether the child's current level of anxiety or opposition is elevated. A recommendation to discontinue ssNPA treatment may be made if the child or family do not make progress with wearing the device in 2-4 weeks (depending on the number of visits during that time). Discontinuation of ssNPA therapy may occur after case consultation with other members of the study team to ensure that all strategies have been considered.

9.5.2 Treatment Discontinuation Criteria

Patient willingness:

During the study, the patient/caregiver has the right to withdraw from the study anytime. The study will provide consultations prior to study withdrawal to understand the issues that the patient encounters.

Adverse events:

Several design measures have been instituted to avoid device failure. If breakage of the ssNPA occurs, there would be the rare, theoretic possibility of airway foreign body. In addition, if there is a breakage or any additional severe adverse event observed in more than 2 patients and attributed to device design, the trial will also be terminated.

9.5.3 Clinical Trial Termination Criteria

The Principal Investigator (PI), Data Safety Monitoring Board (DSMB), National Institutes of Health (NIH), and Institutional Review Board (IRB) officials reserves the right to terminate the clinical trial for safety or administrative reasons at any time.

Conditions that may warrant discontinuation of the trial may include, but are not limited to, the following:

- Discovery of an unexpected, serious or unacceptable risk to the patients enrolled in the study (that is likely related to the device) in greater than 1 patient.
- Decision on the part of the device manufacturer to suspend or discontinue testing, evaluation or development of the study product at any time.

9.6 Device Accountability

All use of the device will be under the direct supervision of the principal investigator or his/her designee. The investigational devices will be clearly labeled as investigational use only, and have a clearly marked serial number for each device, which clinical staff will record upon receipt of the device. The receipt date and serial number will be recorded, and package sterility confirmed. The devices will be individually stored in sterilized pouches and secured in the laboratory in the Lurie Biomedical Engineering Building at the University of Michigan North Campus until dispensed to the patient at Michigan Medicine Pediatric Otolaryngology Clinic.

All records of receipt, use, and disposition of the devices will be maintained by the study team. At the completion of the study, there will be a final reconciliation by study personnel of devices shipped, used, and devices remaining. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused devices.

10.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1 Sample Size

The sample size will be 5 pediatric patients with HUAO for the R61 phase and 40 pediatric patients for the R33 phase.

10.1.1 Statistical power calculation for sample size (R33 phase):

While we have demonstrated resolution of extremely severe OSA in our initial patients with hypotonia, the sample size calculation for the current trial is based on conservative assumptions. We defined a treatment response as meeting both a 50% reduction in AHI (e.g., 12.8 to 6.4) and post-treatment AHI<15 at Week 8. We considered this as the clinically meaningful improvement and designed the study to detect a difference in the proportion of children meeting clinically

meaningful improvement in OSA of 60% in the ssNPA device group vs. 18% in the SoC group. To detect a between-group difference of 60% vs.18%, we will enroll 20 children per arm, for a total of 40 children, which will provide 80% power using a two-sided 0.05 level test. The study power will differ by the various assumptions. In particular, if the treatment response occurs in 15% or 20% of the ScC group enrollees, the proposed sample size will provide 75% and 86% power to detect the respective between-group differences in treatment response. We note that if a patient requires a tracheostomy within the 8 weeks of randomization, the patient will be considered not to have a treatment response. We expect further adjusting the primary analysis for baseline values of AHI will likely increase the power to detect the meaningful difference. For continuous outcomes such as PSQ or PedsQL, the proposed sample size is expected to give 80% power to detect an effect size of 0.89 SD or larger. We conservatively assume up to 20% dropout from the study where neither a tracheostomy nor a PSG is done, and to ensure that a total of 40 children have complete outcome data, we will enroll 50 children.

10.2 Data Analysis

10.2.1 R61 Phase:

Analyses will be descriptive in the R61 phase of the study. The primary aim of the R61 phase is the 2nd generation ssNPA device confirmation and proof of concept that the ssNPA is tolerated and comfortable. For measures obtained using a 10-point scale including tolerability and comfort, we expect the margin of error for the mean estimate with 95% confidence to be 1.24 standard deviation. When tolerability and comfort measures are dichotomized (i.e., considering scores of 7 out of 10 as acceptable), the proposed sample size will give a margin of error of 0.19 for an estimate of proportion with positive responses.

10.2.2 R33 Phase Statistical analysis:

We will summarize subject characteristics by study arm. We will also summarize outcomes data at each assessment time and changes from baseline in outcome measures at each follow-up time by arm using appropriate summary measures including means, standard deviations, and proportions. If the data are highly skewed such as increasing variability with increasing mean, we will consider log-transformation. Primary outcomes will be treatment response at Week 8, defined as a clinically meaningful improvement in AHI of 50% reduction and AHI<15, and primary analytic cohort will be intent-to-treat. For the comparison of treatment response, receiving tracheostomy prior to Week 8 will be considered a treatment response failure. Although post treatment data are collected at Weeks 8 and 16, primary comparative analysis will be done using Week 8 data as the SoC group patients initiating the ssNPA at Week 8 will have self-selected to use the device and are not parallel to those initially randomized to the ssNPA. The between-arm difference in treatment response will be compared using a two-sample proportion test. Secondary outcomes will include various patient and caregiver outcome measures including AHI, PSQ, PedsQL and OSA-18. Improvement in each of these continuous measures will be compared between arms using mixed models with data at both baseline and Week 8 as the dependent variables, participants as random intercepts and an indicator for the ssNPA arm, an indicator for Week 8, and an interaction of Week 8 by ssNPA am as the primary predictors. The parameter of the Week 8 by ssNPA arm interaction term will estimate the ssNPA effect. We will separately

report dropouts by arm and collect data on reasons for dropping out of the study. If dropout rate is more than 10%, for each outcome variable, we will perform an alternate parallel analysis where we will weigh the between-arm response comparisons inversely by the propensity of dropping out, with the propensities estimated separately from a logistic regression predicting dropout using baseline patient characteristics (e.g., age, sex, baseline AHI, treatment arm).

In secondary analyses, we will use linear mixed models and fit longitudinally assessed outcomes data at baseline, Weeks 8 and 16 to assess the long-term effects of ssNPA. For binary treatment response, the outcomes assessed at Week 8 and 16 will be modeled using a generalized mixed model with logit link. The model will include participants as random intercepts and will include the ssNPA arm indicator, categorical time indicators for Weeks 8 and 16, and interactions of Week 8 by arm and Week 16 by arm. A significant interaction of Week 8 by ssNPA arm will provide evidence for ssNPA effect, and showing no difference in the coefficients between the two interaction terms of Week 8 by ssNPA arm and Week 16 by ssNPA arm will indicate NPA effect to remain long-term over the 4-month period. Prior to the longitudinal data modeling, we will graph cross-sectional means of outcome measures (e.g., percentage with treatment response) with SoC group stratified further to those that opted to receive ssNPA at Week 8 vs. not to visualize if their Weeks 8 and 16 data should be treated as a separate group or can be treated as additional data to ssNPA arm data. The data and model will allow us to explore for sub-hypotheses if the number of SoC group patients receiving ssNPA at Week 8 is substantial. We note, however, that the Week 16 outcomes of SoC group patients will be interpreted carefully as they reflect outcomes in participants who opt to use or not use ssNPA after having been exposed to the standard care under a research setting for an 8-week period.

Of critical importance will be subgroup of patients who have OSA severity with AHI>30. These Patients with HUAO and extremely severe OSA are likely to fail surgical interventions other than tracheostomy and as such will be considered “warranting tracheostomy”. Given the proposed sample size and the known prevalence of about 20% of hypotonic patients with severe apnea, we expect a total of about 8-10 patients “warranting tracheostomy”. We will report, by each arm, the number (%) receiving tracheostomy in all study enrollees and in those with baseline AHI>30 by Week 8. We will also report the number (%) receiving tracheostomy in those randomized to ssNPA arm by Week 16. These data will be used for future power calculations to determine sample size requirements for larger trials focused on the utility of the ssNPA in tracheostomy avoidance.

Another important parameter is adherence, which will be reported as percentage of participants using the device at two months after initiation in both the active group (ssNPA) and in the wait list group (SoC) participants who received the device at Month 2. In the active group, we will compare adherence rates between treatment responders (those with >50% reduction in AHI and AHI<15 at Week 8) and non-responders to assess the relationship between adherence and treatment response. However, since clinically meaningful improvement can be accomplished by using ssNPA without the need for continued use of the device for two months, we will carefully analyze the daily

adherence data obtained using diaries to have a better understanding of the relationship between adherence during the first 8 weeks and treatment response.

10.3 Outcome Criteria

10.3.1 R61 Phase:

Criteria	**Goal (out of 5 subjects)**
Device optimization and manufacturing in a clean/sterile manner	100%
Parent/CG reported ease of insertion; >= 5 on Likert scale of 1-10	60%
Child able to tolerate device in place	60%
Child able to maintain device in place during sleep	60%
Parent/CG report of adherence based on diary	60%
Comfort rating >=7 on Likert scale of 1-10	60%

10.3.2 Other Outcome Measures for the R61 Phase

Secondary outcomes will determine change in sleep quality as well as other symptoms of OSA such as snoring and daytime sleepiness. Comparisons between baseline and 8-week outcomes for sleep quality and daytime sleepiness (measured continuously) will be made using paired t-tests with a p-value <0.05 considered statistically significant. Exploratory analyses will determine changes in oxygen saturation nadir, sleep efficiency and possible improvement in sleep architecture such as increase in sleep efficiency, stage N3 and REM sleep. In addition, the insertion protocol will be optimized to make sure that it is safe, effective, and acceptable by parents/caregivers for ssNPA self-insertion. The current sizing protocol for physicians will also be optimized to effectively help physicians determine the proper length for ssNPA for each patient. These protocols will guide the larger clinical trial in R33 phase.

10.3.3 R33 Phase

We anticipate that use of the ssNPA will show clinically meaningful improvement (reduce the AHI by at least 50% and to a level <15) in substantial percentage (>60%) of children with OSA and that the device will be able to be tolerated by greater than 60% of children and parents.

10.3.4 Other Outcome Measures for the R33 Phase

We expect that subjective sleep-related symptoms including impaired sleep quality, snoring, and daytime sleepiness, as well as quality of life for both parent and child will be improved.

10.4 Dropouts/Lost-to-Follow-up

In order to achieve the 95% confidence and statistics specified above, we need a sample size of 5 patients. Thus, we will conservatively assume up to 20% dropout from the study, and to ensure that a total of 5 children have complete outcome data, we will enroll 7 children.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with FDA's Good Clinical Practice regulations.

11.1 Informed Consent

In accordance with the provision of 21 CFR Part 50, each caregiver or subject will provide written informed consent for participation in this study prior to the use of the investigational device.

The study will be explained to the prospective caregiver and subject by the investigator or his designee. The nature of the experimental product will be explained together with potential hazards of the treatment including any possible adverse reactions. The subject will be informed that he/she is free to terminate participation in the study for any reason. One copy of the signed consent form will be retained in the medical record, and one copy will be given to the subject.

11.2 Institutional Review Board

This protocol and the informed consent form will be approved initially and reviewed annually by the University of Michigan Institutional Review Board (IRB). Progress reports will be submitted at the completion of the study or at least once yearly, whichever comes first, to the IRB. Serious adverse events will be reported to the IRB and in accordance with applicable regulations for serious adverse events.

11.3 Protection of Human Subjects

11.3.1. Human Subjects Involvement and Characteristics

This Human Subjects Research meets the definition of Clinical Research.
Human Use Board Approval: All procedures described for the proposed study will be approved by the University of Michigan Medical School Institutional Review Board (IRBMED).
The proposed study will involve recruitment of children with Hypotonic Upper Airway Obstruction (HUAO) and obstructive sleep apnea (OSA) aged 3-21 years. Children with HUAO will undergo a baseline sleep study (polysomnogram) to determine presence of OSA and thus eligibility. Subjective sleep measures and quality of life will also be assessed. Those with an apnea hypopnea index (AHI) of greater than 10 events per hour will be eligible to receive therapy with the self-supported nasopharyngeal airway. Families will be instructed on use of the ssNPA and will encouraged to use it for approximately 8 weeks when the child will undergo a repeat polysomnogram. Thus all children stand to benefit from this novel intervention. However, within the 2-month time period it is highly likely that these children will not yet receive the SoC treatments such as Positive Airway Pressure (PAP) (in our institution it is common for it to be six months from initial referral to PAP titration and approximately 8-10 weeks from the time of a baseline study to a PAP titration). Subjective sleep measures and quality of life assessments will occur for all subjects at the end of each 8-week period. Demographic and relevant medical information will be extracted from medical records. All subjects and their families will be notified that consent to participate is voluntary and can be withdrawn at any time. Written informed consent will be obtained from each parent and assent will be obtained from subjects where appropriate.

Recruitment will occur at practices of otolaryngologists, sleep medicine physicians, and pediatricians as well as via parent support groups. The investigators have worked in such interdisciplinary groups and their staff for almost 20 years to recruit pediatric subjects successfully, achieving targeted goals for three other NIH-funded R01 projects.

Prior to study enrollment, tours of the sleep laboratory will give subjects and families a preview of that environment and equipment used there, reduce any possible fears or anxieties, and give them a good understanding of study requirements in relation to family, school, and job commitments. Technicians experienced with children, including children with developmental disabilities, and anxieties of this age group will conduct sleep studies. One parent will stay with each child during overnight testing to reduce separation anxiety. Spacious pediatric sleep rooms are designed to include a separate bed for the parent. During sleep studies, a physician investigator will always be on call for any unexpected emergencies. Studies will be performed in the 12-bed Michael S. Aldrich Sleep Disorders Laboratory, Division of Sleep Medicine, where a 24-hour technical staff including pediatric and research technologist pods is well prepared to meet the needs of children and families who participate in research. Finally, every effort will be made to ensure, as in the investigators' past NIH-funded pediatric sleep protocols, that this research experience is fun, positive, and rewarding for each subject and family.

Problems with ssNPA use will be preempted in part by thorough education of parents, and children, about the purpose, potential benefits, and importance of nightly adherence. Participating families will be well educated about potential problems, and what to do about them, even before starting ssNPA therapy. The device has demonstrated initial safety and efficacy in a pilot group of 4 patients with severe OSA (apnea/hypopnea index, or AHI, as high as 114/hour). The NPA devices will have a series of sizes (lengths and silicone attachment sizes) available for otolaryngologist to choose. The otolaryngologist will then determine the optimal size for each child to achieve the best fitting and appropriately bypass the obstruction. This will minimize risk for discomfort or irritation. After ssNPA therapy is initiated, contact initially with study team members will occur daily during the first week of using the device and will continue during following weeks if needed and will provide multiple opportunities to detect and correct problems. Use of ssNPA on every night will be encouraged: parents and children will be educated about its importance.

11.3.2. Sources of Research Material.

Clinical data will be obtained for research purposes. Data from polysomnography, ssNPA therapy, and questionnaires will be collected and stored as research data. Information from medical records will be extracted. Access to medical records will be requested from the University of Michigan IRBMed, mainly for any demographic data, medication lists, or other information that might be missing from study-specific forms, and not for collection of any of the main variables under study. Each of the investigators will have access to individually identifiable private information about human subjects. Individuals not on the investigative team will not have access to this information. Written data will be stored in locked cabinets, in locked offices, separate from keys that identify subject names. Electronic data will be stored on password-protected, regularly-backed-up server files and on external hard drives kept securely.

11.3.3. Potential Risks:

Only minimal risks are associated with the subjective sleep measures and quality of life assessments to be administered to children or their parents. Risks associated with polysomnography are relatively small. In preparation for polysomnography, particularly for the first time, placement of the sensors can create transient discomfort or anxiety for some children, especially those with development disabilities. Other risks of the sleep studies include the stress of an unfamiliar environment, stranger anxieties, a night of sleep that may not be as restful as that obtained at home, and cutaneous allergic reaction or irritation that can occur at the site of electrode or tape placement. Finally, as in any research, risks exist for breach of confidentiality and loss of data. Overall, the benefit to the child of sleep study results, and what is almost always a fun, positive, and memorable experience is likely to outweigh potential harm. Almost all children and families (95%) who have completed similar testing protocols at baseline in the past have been happy to repeat them again.

The protocol also calls for subjects to use ssNPA therapy nightly. This requires commitment on the part of each child and parent. However, the treatment is not onerous, and in clinical settings NPA has been used in children of all ages. Our pilot data (under the UM Innovative Care Consent process) demonstrates that the treatment is safe and effective in children with a craniofacial malformation and hypotonia, however, NPA devices are not yet FDA-approved for use. In children with sleep apnea, adenotonsillectomy or use of PAP are the usual therapies and have been shown to improve quality of life. However, in children with HUAO, treatment of OSA presents an extremely difficult challenge, in part due to frequent multilevel upper airway obstruction secondary to anatomic features that can lead to diffuse, circumferential collapse. Thus, many surgical approaches, other than tracheostomy, often fail and a majority of children with HUAO have residual OSA following adenotonsillectomy. This often necessitates treatment with PAP, but the rate of adherence is low in typically developing children and even lower in those with developmental disabilities. Tracheostomy then becomes a final option.

Specific risks from using the ssNPA include blockage of the endotracheal tube with secretions. [redacted]

The risks of completing validated questionnaires about sleep and quality of life are minor.

Finally, participants will reveal personal information about themselves and there is a risk of breach of confidentiality. Participants will be informed of the procedures taken to preserve confidentiality.

The proposed protocol adheres to the ethical principles outlined by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Respect for persons is maintained, as the adult parent or guardian with full capacity will provide written informed

consent, a child over the age of 8 years and able to understand the study will provide written assent were appropriate, and a younger child will give verbal assent. The principle of beneficence is respected as for each participant the potential for personal benefit from this study will outweigh the small risks involved. This study will not subject any child to tests or treatments that stand no chance to benefit him or her personally. No child will be deprived of needed medical care. Agreement to participate in this research will not prevent any family from withdrawing at any time. Lastly, the principle of justice is respected because the population to be studied will be exactly that which stands to gain most from the results of the study.

11.3.4. Adequacy of Protection Against Risk:

Subjects will be recruited from Michigan Medicine clinics as well as the larger community, which may or may not include patients of the health system. The details of the study will be explained, and families will have ample opportunity to ask questions. Families will be counseled about the potential risks of not treating OSA. Potential participants and their families will be informed that the study will involve an overnight sleep study. Written informed consent and child assent (where appropriate) will be obtained prior to enrollment. Participation is voluntary and can be terminated at any time.

The most common risk is discomfort during adjustment to ssNPA use. We plan several steps to minimize this, the main step is to determine the ssNPA device size by the otolaryngologist via the endoscopic examination to provide the optimal fitting and anatomic position to appropriately bypass the obstruction. Furthermore, an experienced otolaryngologist will perform the initial insertion and teach caregivers how to use the ssNPA. A suction device will be provided to all families to prevent the ssNPA becoming blocked with secretions. Families will be instructed how to use it using a step-by-step desensitization protocol that will be provided to them and the study nurse will be available for any questions or concerns. Primary care physicians will be informed of their patient's enrolment in the study and will be informed if any issues arise with use of the ssNPA. Subjects will have almost daily contact initially with the research team, which typically tapers to a weekly telephone call to discuss any problems or questions. This exceeds generally available standard of care in clinical practice but will optimize safety and yet remain generalizable to clinical settings.

Standard clinical protocols will be followed for anything that raises clinical concern. Children may or may not remain in the study, depending on the finding.

The risks of completing validated questionnaires about sleep and quality of life are minor. However, if children are found to have clinical levels of depression, standard protocols for mental health concerns (e.g., severe depression or suicidal ideation) will be followed for anything that raises clinical concern.

The potential risks of breached confidentiality are serious, and we have taken a number of special precautions. First, the research team has already completed training sessions on all stages of confidentiality, including personal contact, telephone contact, and data records. The importance of maintaining confidentiality will be emphasized at all times. Avoidable breaches in confidentiality by staff members will be grounds for dismissal. However, given the nature of the

proposed study, primary care physicians will be informed of their patient's participation as ssNPA may directly impact their clinical care. In the research database participant identifying information will be kept separate from their responses to the questionnaires. Information relating to polysomnography and NPA therapy will also be de-identified when entered into the research database (and when ssNPA therapy is initiated). Identification codes will be assigned to participants. These codes will also be kept separate from identifying information, with only the PI and other key personnel having access to this de-coding information.

Concerns about confidentiality continue after data collection is completed. Data, coded only with unique identifying code numbers, will be stored separately from identifying information. All data will be sorted in locked files or computers with password access, accessible only to the PIs and key study personnel. All published reports will contain data reported either in aggregate form (where no individual responses can be identified) or in composite individual examples that are constructed so that identification is not possible. In addition, all levels of staff will have completed the computer based human subjects protection training, including special attention to vulnerable populations. All investigators have already completed certification of this training. Rigorous confidentiality procedures have been planned to minimize the risk of breaches. Therefore, there is minimal risk that confidentiality will be violated. The limits of confidentiality also will be described explicitly by research personnel.

Participation in the study is voluntary and families can withdraw at any time without their child's clinical care being affected.

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

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

11.3.5. Potential Benefit:

All children stand to benefit by being in this trial by reduction of the severity of OSA. We anticipate that the ssNPA device will provide significant relief from airway obstruction

11.4. Data and Safety Monitoring Plan

The goal of the data and safety monitoring plan (DSMP) will be to protect patient safety and ensure the integrity and validity of the data. We will achieve this with a protocol designed to monitor and report both adverse (AEs) and serious adverse events (SAEs) specifically related to the protocol evaluations and ssNPA treatment, monitor study progress, assess appropriateness of continuing or stopping the trial, ensure protocol compliance and data accuracy, and prevent biased interpretation of data or conflict of interest. Our DSMB will be comprised of a multidisciplinary team. No member on the team will have outside conflicts of interest as relates to the study. We will register this trial in a clinical trial registry that meets NIH approval. We will elaborate and modify this DSMP as necessary in working with the NIH to formulate acceptable approaches.

Data and safety monitoring for this randomized, controlled, single-site clinical trial comparing ssNPA treatment to standard of care in children with Hypotonic Upper Airway Obstruction (HUAO) and OSA will be accomplished in part by a Data and Safety Monitoring Board (DSMB). The board will be composed of individuals with expertise relevant to this study, its participants, or the evaluations and interventions that are planned. The DSMB board members will be external to the investigators, external to the University of Michigan, and otherwise uninvolved in this research. The DSMB will be assembled and guided with assistance from the relevant Program Officer at the NIH. The DSMB will convene, at least annually, and generally by phone, to review and make recommendations regarding recruitment and retention, AEs and SAEs, any treatment safety concerns, and data quality or integrity. The Principal Investigators will review, grade, and report any adverse events, ORIOs, or unanticipated problems, with the assistance of the Project Manager, to the IRBMED, the DSMB, and the NIH program officer as required by the approved study-specific DSMP.

11.4.1 Adverse Events

Complications or adverse events that are observed by the investigator or reported by the subject should be recorded on the CRFs. For all adverse events and complications, a description of the event, date first observed, any action taken, and ultimate outcome will be recorded. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the causal relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s). Adverse effects felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigators and NIH. Any questions as to the expectedness of an adverse event will be discussed with the PI and/or the DSMB.

Device safety will be determined by adverse events evaluation. Any possibly-related adverse events (e.g. nasal skin necrosis or device displacement) will be evaluated through clinical visits and caregiver's feedback using standardized case report forms. The anticipated Adverse events are as follows:

- Skin irritation/allergy
- Bloody nose
- Difficulty breathing
- Necrosis
- Inflammation
- Persistent uncomfortable sensation (e.g. itch)
- Persistent gagging
- Airway foreign body or airway compromise (serious)
- Accidental dislodgment

The PI will review and assess AEs and SAEs for nature, seriousness, severity, frequency, expectedness, and relatedness to the study interventions. Information on AEs or SAEs or other significant reportable occurrences on this protocol will be reported to the Data Safety Monitoring Board. The DSMB will be responsible for (1) periodic review and evaluation of participant safety, recruitment and retention, and study conduct, and for (2) recommendations for continuation, modification, or termination of this clinical trial. The DSMB will be notified of project-related, medical or psychological conditions, or adverse and serious adverse events that may require intervention. Protections against risks in the proposed research will include those detailed in the Human Subjects Protection section.

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

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

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

11.4.2 Principal Investigator Responsibilities

The Principal Investigator (PI) will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a *serious adverse effect*.

In accordance with 21 CFR Part 812.150(a)(1) and (b)(1), the PI shall promptly report the results of an evaluation of any serious and unanticipated adverse device effect to the University of Michigan IRBMED as soon as possible, but not later than 10 working days after the PI first receives notice of the effect. Thereafter, the PI shall submit such additional reports concerning the effect to the sponsor of the trial and as the FDA requests. Complications and non-serious or anticipated adverse events should be documented and tabulated but need not be submitted by the PI to the sponsor of the trial or the FDA as individual reports.

11.4.3 Investigator Responsibilities

All serious and unanticipated adverse events should be reported to the PI within 24 hours of first learning of the event. Those that are determined to be serious and unanticipated after DSMB review should also be reported to the IRB as required according to the reporting requirements of the University of Michigan IRBMED.

11.5 Monitoring

To assure adequate protection of the rights of human subjects, per 21 CFR §812.40, 812.43 and 812.46, this study will be monitored by the University of Michigan Institute of Clinical and health research (MICHR). Routine monitoring will be scheduled at appropriate intervals, with more frequent visits occurring at the beginning of the study. A site activation visit will take place, followed by routine monitoring visits. Additional visits can be scheduled at the request of the investigative team.

The established monitoring plan will ensure the quality and integrity of the data throughout the study conduct to verify adherence to the protocol, completeness and accuracy of study data and samples collected, dispensing and inventory of the device, and compliance with regulations.

11.5.1 Data Safety Monitoring Board (DSMB)

The annual report from the investigators to the DSMB will include summaries of enrollment, subject withdrawals, and numbers of subjects who have completed the protocol. Any problems with data collection, quality, analysis, management, loss, or confidentiality will be described, along with any consequent protocol changes and options still available to remedy the concerns. Interim data analysis, to assess appropriateness of trial completion, is not anticipated. Risks of ssNPA devices are small, potential benefits are large, and harm to participants from completion of the trial with the full sample size is not anticipated.

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

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

11.5.2 Blinding Plan

Per DSMB recommendations aggregate and stratified outcomes will be revealed only to the unblinded statisticians with a firewall related to outcomes between statistician and investigators. Dr. Zopf will be blinded to all aggregate/stratified outcomes and Dr. O'Brien will be blinded to polysomnography and quality of life outcomes.

11.6 Source Documents / Case Report Forms

Adequate records will be maintained for the study including subject medical and surgical records, signed ICFs, and device use records. All original source documentation will remain at the investigative site. Study data that are stored at the investigator site in any electronic medical records system, including measurements that are obtained electronically, will be printed and retained in the study files.

All study data will be recorded onto CRFs (electronic or paper) designed for the study. If paper CRFs are used, copies of the CRFs will be retained with the investigator's study files.

11.7 Protocol Deviation

The investigator will not deviate from the protocol without prior IRB and NIH approval, unless such deviation is necessary to manage a medical emergency. The investigator will notify the IRB and the NIH of any protocol deviation to protect the life, or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event any later than 5 working

days after the emergency occurred. All other revisions and/or amendments to the protocol that affect subject treatment, study outcome, or subject safety should be submitted in writing to the IRB for approval prior to implementation. The investigator should maintain a record of all protocol deviations showing the dates of, and the reason for, each protocol deviation.

11.8 Summary of Phases

11.8.1 R61 Phase:

In the R61 Phase, we will recruit up to 5 children with hypotonic collapse aged between 3-21 years who have had a sleep study at the Sleep Disorders Laboratory for clinical purposes and were diagnosed with severe OSA (AHI>10). Families will be invited to participate in the study and the PI or trained otolaryngologist designee will explain the ssNPA as a novel treatment option for OSA. For those families who are willing to participate, consent and assent (where appropriate) will be obtained and several sleep and quality of life assessments will be completed. Drs Zopf or Kirkham will then perform the device fitting and confirm the optimal anatomy position for each child. Families will be given information about strategies to help children become familiar with the device and will be provided with contact details of the study nurse who will be available to help families. After approximately 8 weeks, a sleep study will be conducted to quantify the change in AHI with the ssNPA in place. Subjective sleep questionnaires and the quality of life assessments will also be repeated. During this phase we will optimize the development of the ssNPA device as well as optimize the delivery of the desensitization protocol. At the end of the R61 phase we will be ideally positioned to launch a randomized trial of the ssNPA in the R33 phase.

11.8.2 R33 Phase:

In the R33 Phase, we will recruit 40 children with HUAO using the same inclusion/exclusion criteria as delineated above. At enrollment all families will complete the questionnaire battery as previously described and children will undergo a baseline polysomnogram. Those children with an AHI>10 will be randomized 1:1 to receive the ssNPA device or standard of care in a crossover design such that all children stand to benefit. Those randomized to ssNPA will be given the ssNPA device to use at home for approximately 8 weeks, at which time a repeat polysomnogram will be conducted. As with the active group, a polysomnogram will occur 8 weeks after randomization for waitlist control group for primary outcome assessment. The waitlist control group will then be offered the ssNPA device and a further polysomnogram will be performed after an additional 8 weeks. Subjective sleep questionnaires and quality of life assessments will also be obtained at each time point. Written informed consent and child assent (where appropriate) will be obtained prior to enrollment. Participation is voluntary and can be terminated at any time.

11.9 Dissemination plan

As Responsible Party, we will share information about this trial via timely registration, updates, and results reporting in ClinicalTrials.gov in accordance with NIH policy. The informed consent documents used for this/these trial(s) will include statements to inform participants that information about the trial will be posted in ClinicalTrials.gov. The University of Michigan's Human Research Protections Program (HRPP) Operations Manual is the primary location where

rules, policies, practices, and guidance pertaining to the University's HRPP are provided, including Section 11 (H) which addresses the requirements to register trials and report results. Compliance with these provisions is monitored by designated components of the UM HRPP. Moreover, these data will also be shared at national conferences and via publications in medical journals and the underlying primary data will be made as widely and freely available as possible while safeguarding the privacy of participants and protecting confidential and proprietary data.

11.9.1 ClinicalTrials.gov

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

12 REFERENCES

1. Lumeng JC, Chervin RD. Epidemiology of Pediatric Obstructive Sleep Apnea. Proceedings of the American Thoracic Society. 2008;5(2):242-52. doi: 10.1513/pats.200708-135MG. PubMed PMID: 18250218.

2. Marcus CL, Brooks LJ, Ward SD, Draper KA, Gozal D, Halbower AC, Jones J, Lehmann C, Schechter MS, Sheldon S, Shiffman RN, Spruyt K. Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome. Pediatrics. 2012;130(3):e714-e55. doi: 10.1542/peds.2012-1672.

3. Park JS, Chan DK, Parikh SR, Meyer AK, Rosbe KW. Surgical outcomes and sleep endoscopy for children with sleep-disordered breathing and hypotonia. International Journal of Pediatric Otorhinolaryngology. 2016;90:99-106. doi: https://doi.org/10.1016/j.ijporl.2016.09.004.

4. ADAMS N, STRAUSS M, SCHLUCHTER M, REDLINE S. Relation of Measures of Sleep-Disordered Breathing to Neuropsychological Functioning. American Journal of Respiratory and Critical Care Medicine. 2001;163(7):1626-31. doi: 10.1164/ajrccm.163.7.2004014. PubMed PMID: 11401885.

5. Amin RS, Carroll JL, Jeffries JL, Grone C, Bean JA, Chini B, Bokulic R, Daniels SR. Twenty-four–hour Ambulatory Blood Pressure in Children with Sleep-disordered Breathing. American Journal of Respiratory and Critical Care Medicine. 2004;169(8):950-6. doi: 10.1164/rccm.200309-1305OC. PubMed PMID: 14764433.

6. Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, Guilleminault C. Inattention, Hyperactivity, and Symptoms of Sleep-Disordered Breathing. Pediatrics. 2002;109(3):449-56. doi: 10.1542/peds.109.3.449.

7. Gozal D. Sleep-Disordered Breathing and School Performance in Children. Pediatrics. 1998;102(3):616-20. doi: 10.1542/peds.102.3.616.

8. Gozal D, Capdevila OS, Kheirandish-Gozal L. Metabolic Alterations and Systemic Inflammation in Obstructive Sleep Apnea among Nonobese and Obese Prepubertal Children. American Journal of Respiratory and Critical Care Medicine. 2008;177(10):1142-9. doi: 10.1164/rccm.200711-1670OC. PubMed PMID: 18276939.

9. Gozal D, Kheirandish-Gozal L. Cardiovascular Morbidity in Obstructive Sleep Apnea. American Journal of Respiratory and Critical Care Medicine. 2008;177(4):369-75. doi: 10.1164/rccm.200608-1190PP. PubMed PMID: 17975198.

10.Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, Kaditis AG, Splaingard D, Splaingard M, Brooks LJ, Marcus CL, Sin S, Arens R, Verhulst SL,

Gozal D. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. Am J R espir Crit Care Med. 2010 Sep 1; 182(5):676-83.

11. Hawkins S, Jensen E, Friedman NR. Correlates of pediatric CPAP adherence. Journal of clinical sleep medicine, 2016;12(6):879–884.

12. Marcus CL, Rosen G, Ward SLD, Halbower AC, Sterni L, Lutz J, Stading PJ, Bolduc D, Gordon N. Adherence to and Effectiveness of Positive Airway Pressure Therapy in Children With Obstructive Sleep Apnea. Pediatrics. 2006;117(3):e442-e51. doi: 10.1542/peds.2005-1634.

13. Funamura JL, Yuen S, Kawai K, Gergin O, Adil E, Rahbar R, Watters K. Characterizing mortality in pediatric tracheostomy patients. The Laryngoscope. 2017;127(7):1701-6. doi: 10.1002/lary.26361.

14. Dal'Astra APL, Quirino AV, Caixêta JAdS, Avelino MAG. Tracheostomy in childhood: review of the literature on complications and mortality over the last three decades. Brazilian Journal of Otorhinolaryngology. 2017;83(2):207-14.

15. Rizzi CJ, Amin JD, Isaiah A, Valdez TA, Jeyakumar A, Smart SE, Pereira KD. Tracheostomy for Severe Pediatric Obstructive Sleep Apnea: Indications and Outcomes. Otolaryngology–Head and Neck Surgery. 2017;157(2):309-13. doi: 10.1177/0194599817702369. PubMed PMID: 28417683.

16. Cohen SR, Suzman K, Simms C, Burstein FD, Riski J, Montgomery G. Sleep apnea surgery versus tracheostomy in children: an exploratory study of the comparative effects on quality of life. Plast Reconstr Surg. 1998;102(6):1855-64. doi: 10.1097/00006534-199811000-00008. PubMed PMID: 9810979.

17. Atanelov Z, Rebstock SE. Nasopharyngeal Airway. [Updated 2018 Dec 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan.

18. Chang, A.B., I.B. Masters, G.R. Williams, M. Harris, and M.C. O'Neil, A modified nasopharyngeal tube to relieve high upper airway obstruction. Pediatric Pulmonology, 2000. 29(4): p. 299-306.

19. F. Abel, Y. Bajaj, M. Wyatt, C. Wallis, The successful use of the nasopharyngeal airway in Pierre Robin sequence: an 11-year experience, Arch. Dis. Child. 97 (4) (2012) 331–334.

20. Grube PJ, Fan D, Pothula VR, Vonfrolio CT, Tsang D, Hoffman D. Prevention of aspiration of nasopharyngeal airway. Indian J Anaesth. 2010;54(1):74. doi:10.4103/0019-5049.60511.

21. Okuno K, Minagi HO, Ikai K, Ai EM, Takai E, Fukatsu H, Uchida Y, Sakai T. The efficacy of nasal airway stent (Nastent) on obstructive sleep apnoea and prediction of treatment outcomes. Oral Rehabil 2019 Jan;46(1):51-57.

22. American Academy of Sleep Medicine Scoring Manual (AASM). 2017;version 2.4

23. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Medicine 2000;1(1):21-32.

24. Franco RA, Rosenfeld RM, Rao M. Quality of life for children with obstructive sleep apnea. Otolaryngology–Head and Neck Surgery. 1999;121(2_suppl):P98-P9. doi: 10.1016/s0194-5998(99)80138-7.

25. Melendres CS, Lutz JM, Rubin ED, Marcus CL. Daytime Sleepiness and Hyperactivity in Children With Suspected Sleep-Disordered Breathing. Pediatrics. 2004;114(3):768-75.

26. Varni JW, Katz ER, Seid M, Quiggins DJL, Friedman-Bender A, Castro CM. The Pediatric Cancer Quality of Life Inventory (PCQL). I. Instrument Development, Descriptive Statistics, and Cross-Informant Variance. Journal of Behavioral Medicine. 1998;21(2):179-204.

27. Donenberg G, Baker BL. The impact of young children with externalizing behaviors on their families. Journal of Abnormal Child Psychology. 1993;21(2):179-98.

INSERTION AND CARE OF SELF SUPPORTED NASOPHARYNGEAL AIRWAY (ssNPA)

CAREGIVER TEACHING RECORD

Patient Name:_____ Caregiver #1:_____

MRN:_____ Caregiver #2:_____

Required Skill	Date Explained/Observed	Date caregiver completed (initial) Caregiver #1 Caregiver #2
Demonstrate understanding of reasoning for using ssNPA. Understand anatomy of nasopharynx of child.		
Gather equipment needed for procedure.		
Assess need for nasal suctioning before removing old tube or placing new device.		
Demonstrate safe nasal/ssNPA suctioning.		
Able to remove existing ssNPA.		
Wet with saline and insert new ssNPA.		
Assess need for nasal suctioning after insertion of ssNPA and perform if needed.		
Demonstrate understanding of when ssNPA may be blocked, and how to manage and prevent.		
Demonstrate understanding of when to seek medical attention.		
Demonstrate understanding of cleaning and storage of ssNPA.		
Attend CPR training.		

First two weeks – daily phone calls

Baseline

Good morning/afternoon I am _____ from the University of Michigan Mott Children's hospital. The purpose of this call is to follow up with you regarding you or your child's experience with the ssNPA last night.

Did you fill out the daily survey from last night?

*If yes** [skip to the bottom to the adverse events evaluation]

*If no** Alright, well then I have a few questions to ask you.

Did you have any difficulty with using the ssNPA last night? *If answers yes** Could you describe those difficulties to me?
How long did your child use the ssNPA last night?
How did your child tolerate the device?
Did you have to re-insert or re-adjust the device during the night? If so, how many times did you have to get up to do this?
What was the level of perceived comfort of your child as they wore the device during the night or, if applicable, during the day.
Did the frequency and/or amplitude of your child's snores change last night?
Did you notice any apneas during the night?
How did your child sleep overall?
Does your child seem more rested today?

Did you have any difficulties or adverse events with the device? Did you notice any nosebleeds, irritation, or any of the adverse events listed on your instruction form during your child's use of the device?

Tonight, you will insert the ssNPA device again for overnight use. Remember that if your child feels comfortable with the device in place in the morning, you can leave it in place during the daytime as well. Please fill out the daily survey and we will call you tomorrow to follow-up with you as well.

Do you have any other comments/concerns/questions?

Thank you for your time.

Weeks 3-8 – weekly phone calls

Good morning/afternoon I am _____ from the University of Michigan Mott Children's hospital. The purpose of this call is to follow up with you regarding you or your child's experience with the ssNPA over the past week.

Did you fill out the weekly survey for this week?

*If yes** [skip to the bottom to the adverse events evaluation]

*If no** Alright, well then I have a few questions to ask you.

Did you have any difficulty with using the ssNPA over this past week? *If answers yes** Could you describe those difficulties to me?
On average, how long did your child use the ssNPA each night/day?
How has your child been tolerating the device?
Did you have to re-insert or re-adjust the device during the night? If so, on average how many times did you have to get up to do this?
What was the level of perceived comfort of your child as they wore the device during the night or, if applicable, during the day.
Did the frequency and/or amplitude of your child's snores change over the week?
Did you notice any apneas during the night?
How has your child been sleeping overall?
Does your child seem more rested during the day?

Did you have any difficulties or adverse events with the device? Did you notice any nosebleeds, irritation, or any of the adverse events listed on your instruction form during your child's use of the device?

Any other comments or concerns about usage that you would like to bring up?

Thank you very much for your time. I will follow up with you again next week.

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Appendix I

Subject ID ☐☐☐☐

Today's date:_____

ssNPA User Feedback Questionnaire – DAY ONE

Thank you for participating in the ssNPA sleep study. Please let us know about you and your child's experience last night/yesterday using the ssNPA device by circling responses below:

1. Device insertion was....

   1 - Extremely difficult
   2 – Difficult
   3 – Neutral
   4 – Easy
   5 - Extremely easy

2. Once placed, the device was...

   1 – Not tolerated
   2 – Poorly tolerated
   3 - Neutral
   4 – Tolerated
   5 – Well-tolerated

3. During the night, the device came out completely and needed to be re-inserted...

   1 – Very frequently
   2 – Frequently
   3– Sometimes
   4 – Rarely
   5 – Not at all

4. During the night, the device came out partially and needed to be adjusted...

   1 – Very frequently
   2 – Frequently
   3 – Sometimes
   4 – Rarely
   5 – Not at all

5. On a typical night, how many times do you usually get up in the middle of the night to check on/adjust your sleeping child and/or their sleep apnea device: ___

6. With the ssNPA, how many times did you have to get up during the night to optimize position of the device: ___

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Subject ID ☐☐☐☐

7. Please rate the level perceived comfort of your child wearing the device during the night…

   1 – Very uncomfortable
   2 – Uncomfortable
   3 – Neutral
   4 – Comfortable
   5 – Very comfortable

8. If applicable, please rate the perceived comfort of the device during the day…

   1 – Very comfortable
   2 – Uncomfortable
   3 – Neutral
   4 – Comfortable
   5 – Very comfortable

9. While using the device, my child's sleep was

   1 – Much less restful
   2 – Less restful
   3 - Stable
   4 – More restful
   5 – Much more restful

10. While using the device, my child's snoring occurred

    1 – Much less often
    2 – Less often
    3 – Unchanged
    4 – More often
    5 – Much more

11. While using the device, my child's snores were…

    1 – Much louder
    2 – Louder
    3 – Unchanged
    4 – Quieter
    5 – Much quieter

12. In the morning, my child appeared…

    1 – Much more tired
    2 – More tired
    3 – Unchanged
    4 – Less tired
    5 – Much less tired

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Subject ID | | | | |

Do you have any other comments or suggestions that you would like to share regarding your experience using the ssNPA?

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Appendix J

Subject ID ☐☐☐☐

Today's date:_____

ssNPA User Feedback Questionnaire - DAILY

Thank you for participating in the ssNPA sleep study. Please let us know about you and your child's experience last night/yesterday using the ssNPA device by circling responses below:

1. Device insertion was....

   1 - Extremely difficult
   2 – Difficult
   3 – Neutral
   4 – Easy
   5 - Extremely easy

2. Once placed, the device was...

   1 – Not tolerated
   2 – Poorly tolerated
   3 - Neutral
   4 – Tolerated
   5 – Well-tolerated

3. During the night, the device came out completely and needed to be re-inserted...

   1 – Very frequently
   2 – Frequently
   3– Sometimes
   4 – Rarely
   5– Not at all

4. During the night, the device came out partially and needed to be adjusted...

   1 – Very frequently
   2 – Frequently
   3 – Sometimes
   4 – Rarely
   5 – Not at all

5. With the ssNPA, how many times did you have to get up during the night to optimize position of the device: ___

6. Please rate the level perceived comfort of your child wearing the device during the night...

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Subject ID ☐☐☐☐

1 – Very uncomfortable
2 – Uncomfortable
3 – Neutral
4 – Comfortable
5 – Very comfortable

7. If applicable, please rate the perceived comfort of the device during the day…

   1 – Very uncomfortable
   2 – Uncomfortable
   3 – Neutral
   4 – Comfortable
   5 – Very comfortable

8. While using the device, my child's sleep was…

   1 – Much less restful
   2 – Less restful
   3 - Stable
   4 – More restful
   5– Much more restful

9. While using the device, my child's snoring occurred…

   1 – Much less often
   2 – Less often
   3 – Unchanged
   4 – More often
   5 – Much more

10. While using the device, my child's snores were…

    1 – Much louder
    2 – Louder
    3 – Unchanged
    4 – Quieter
    5 – Much quieter

11. In the morning, my child appeared…

    1 – Much more tired
    2 – More tired
    3 – Unchanged
    4 – Less tired
    5– Much less tired

Do you have any other comments or suggestions that you would like to share regarding your experience using the ssNPA?

_____

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Subject ID | | | | |

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Appendix K

Subject ID ☐☐☐☐

Today's date: _____

ssNPA User Feedback Questionnaire - WEEKLY

Thank you for participating in the ssNPA sleep study. Please let us know about you and your child's experience OVER THE PAST WEEK using the ssNPA device by circling responses below:

1. Device insertion was....

   1 - Extremely difficult
   2 – Difficult
   3 – Neutral
   4 – Easy
   5 - Extremely easy

2. Once placed, the device was...

   1 – Not tolerated
   2 – Poorly tolerated
   3 - Neutral
   4 – Tolerated
   5 – Well-tolerated

3. During the night, the device came out completely and needed to be re-inserted...

   1 – Very frequently
   2 – Frequently
   3– Sometimes
   4 – Rarely
   5 – Not at all

4. During the night, the device came out partially and needed to be adjusted...

   1 – Very frequently
   2 – Frequently
   3 – Sometimes
   4 – Rarely
   5 – Not at all

5. With the ssNPA, how many times did you have to get up on average during the night to optimize position of the device: __

6. Please rate the level perceived comfort of your child wearing the device during the night...

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Subject ID ☐☐☐☐

1 – Very uncomfortable
2 – Uncomfortable
3 – Neutral
4 – Comfortable
5 – Very comfortable

7. If applicable, please rate the perceived comfort of the device during the day…

   1 – Very uncomfortable
   2 – Uncomfortable
   3 – Neutral
   4 – Comfortable
   5 – Very comfortable

8. While using the device, my child's sleep was

   1 – Much less restful
   2 – Less restful
   3 - Stable
   4 – More restful
   5– Much more restful

9. While using the device, my child's snoring occurred…

   1 – Much less often
   2 – Less often
   3 – Unchanged
   4 – More often
   5 – Much more

10. While using the device, my child's snores were…

    1 – Much louder
    2 – Louder
    3 – Unchanged
    4 – Quieter
    5 – Much quieter

11. In the morning, my child appeared…

    1 – Much more tired
    2 – More tired
    3 – Unchanged
    4 – Less tired
    5– Much less tired

Do you have any other comments or suggestions that you would like to share regarding your experience using the ssNPA?

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Subject ID ☐☐☐☐

ADVERSE EVENT SUMMARY

Study ID: _____

Study Arm: ☐ Not Randomized ☐ ssNPA treatment Arm ☐ SoC Arm

Informant/Source: ☐ mother ☐ father ☐ guardian ☐ medical record
☐ study team ☐ other_____

Date of Report: _____
mm/dd/yyyy

Person Completing Report: _____

Assessment type: ☐ Systematic ☐ Nonsystematic

Event: _____

Organ System:

☐ Blood and lymphatic system disorders
☐ Cardiac disorders
☐ Congenital, familial and genetic disorders
☐ Ear and labyrinth disorders
☐ Endocrine disorders
☐ Eye disorders
☐ Gastrointestinal disorders
☐ General disorders
☐ Hepatobiliary disorders
☐ Immune system disorders
☐ Infections and infestations
☐ Injury, poisoning and procedural complications
☐ Investigations
☐ Metabolism and nutrition disorders
☐ Musculoskeletal and connective tissue disorders
☐ Neoplasms benign, malignant and unspecified (including cysts and polyps)
☐ Nervous system disorders
☐ Pregnancy, puerperium and perinatal conditions
☐ Psychiatric disorders
☐ Renal and urinary disorders
☐ Reproductive system and breast disorders
☐ Respiratory, thoracic and mediastinal disorders
☐ Skin and subcutaneous tissue disorders
☐ Social circumstances
☐ Surgical and medical procedures
☐ Vascular disorders

Date(s) of Occurrence: _____
mm/dd/yyyy

Type of Event: ☐ AE ☐ ORIO ☐ Unanticipated Problem

Expectedness: ☐ Expected AE ☐ Unexpected AE

Seriousness: ☐ Nonserious AE ☐ Serious AE (check category below & complete SAE form)

- ☐ death
- ☐ life-threatening
- ☐ hospitalization-initial or prolonged
- ☐ disability /incapacity
- ☐ congenital anomaly / birth defect
- ☐ required intervention to prevent permanent impairment
- ☐ other:_____

Severity or Grade (0-5):

☐ 0 - No adverse event

☐ 1-Mild AE: No treatment needed: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

☐ 2-Moderate AE: Resolved with treatment: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning

☐ 3-Severe AE: Inability to carry on normal activities, required professional medical attention: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other professional medical treatment; they are usually incapacitating.

☐ 4-Life-threatening or disabling AE

☐ 5-Fatal AE

Attribution/Relatedness:

- ☐ Definitely related
- ☐ Probably related
- ☐ Possibly related
- ☐ Unlikely to be related
- ☐ Definitely not related
- ☐ Unknown

Description of Event:

Treatment:

Outcome:

Date Resolved: _____
mm/dd/yyyy

Additional Comments:

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Appendix M

Subject ID ☐☐☐☐

ssNPA Sleep Study

Today's date:

ssNPA User Feedback Questionnaire

Thank you for participating in the ssNPA sleep study. Based on your experiences over the last couple of months, please let us know about you and your child's experience using the ssNPA:

1. Overall, please rate the ease of insertion of the ssNPA:

Extremely easy 1 2 3 4 5 6 7 8 9 10 Extremely difficult

2. Overall, please rate your child's comfort with the device:

Extremely uncomfortable 1 2 3 4 5 6 7 8 9 10 Extremely comfortable

3. Please rate your child's overall sleep quality:

Worse sleep 1 2 3 4 5 6 7 8 9 10 Improved sleep

4. Overall, please rate your child's behavior during the day after using the ssNPA:

Worse than normal 1 2 3 4 5 6 7 8 9 10 Better

5. Please rate how you think the ssNPA works for your child's sleep:

Not effective 1 2 3 4 5 6 7 8 9 10 Effective

6. How likely are you to use this device for your child?

Highly unlikely 1 2 3 4 5 6 7 8 9 10 Definitely

Please provide any comments or suggestions you have regarding the device:

_____

_____

_____

_____