A PILOT STUDY TO EVALUATE SAFETY AND EFFICACY OF THE HYPOGLOSSAL NERVE STIMULATOR IN ADOLESCENTS WITH DOWN SYNDROME AND OBSTRUCTIVE SLEEP APNEA

Protocol Number: 14-146H
Sponsor-Investigator: Christopher Hartnick, MD
Funded By: Inspire Medical Systems

Device: Inspire Upper Airway system
IDE: G140209
Device has prior FDA approval (PMA and IDE P130008, G080122)
NCT 02344108

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Document History Summary

Version #	Version Date
9.5	08 May 2020
9.0	05 Jul 2019
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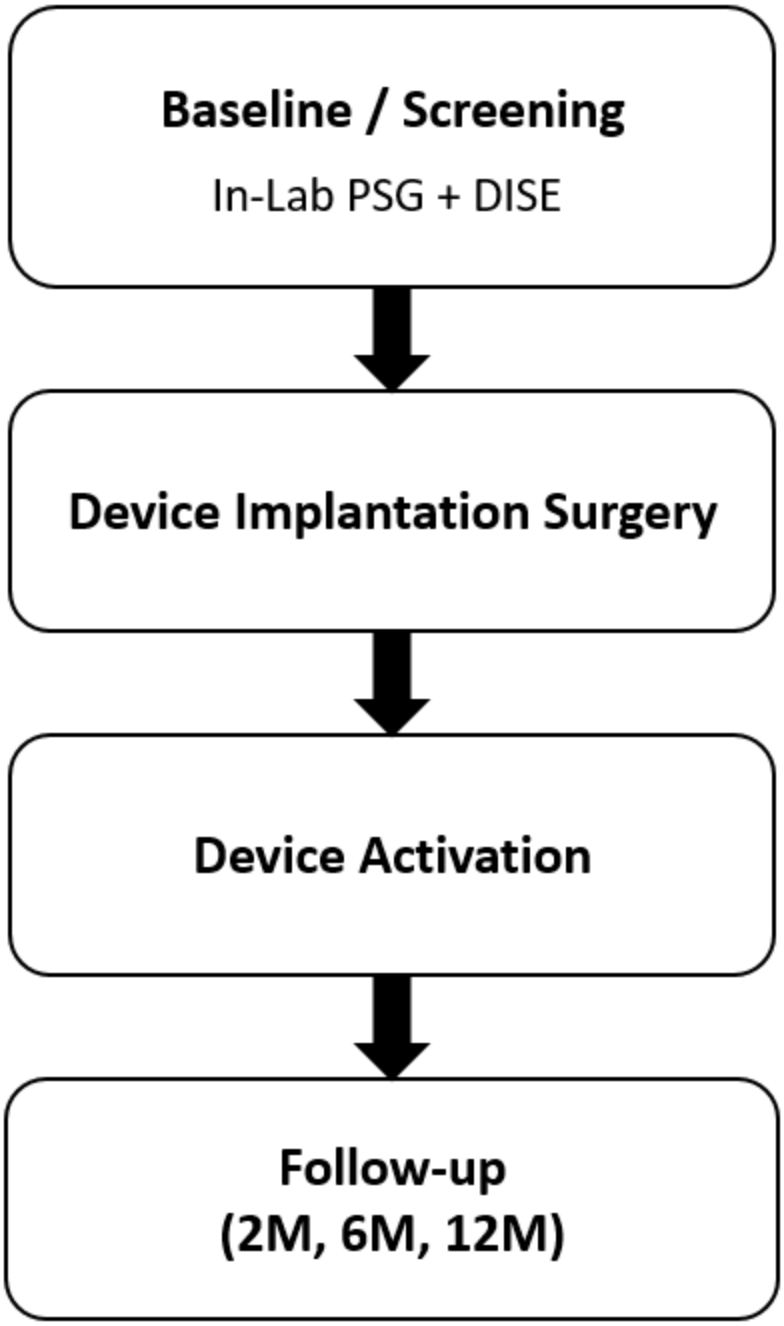
Acronyms & Abbreviations

Term	Meaning
AE	Adverse Event
AHI	Apnea/Hypopnea Index
BMI	Body Mass Index
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
DHHS	Department of Health and Human Services
DISE	Drug Induced Sleep Endoscopy
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
MEEI	Massachusetts Eye and Ear
MOP	Manual of Procedures
OHRP	Office for Human Research Protections
OSA	Obstructive Sleep Apnea
OSA-18	Obstructive Sleep Apnea-18 Questionnaire
PI	Principal Investigator
PSG	Polysomnograpy
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem

Schema


Baseline / Screening
In-Lab PSG + DISE
Device Implantation Surgery
Device Activation
Follow-up
(2M, 6M, 12M)

Protocol Summary

Title:	A pilot study to evaluate safety and efficacy of the hypoglossal nerve stimulator in adolescents with Down syndrome and obstructive sleep apnea
Investigational Device:	Inspire® Upper Airway Simulation System, Model 3028 IPG (previously Model 3024 IPG)
Study Design:	This is a multicenter, prospective, single-arm study of an implantable device for the treatment of obstructive sleep apnea in patients with Down syndrome and previous treatment of adenotonsillectomy.
Accrual Goal:	Up to 42
Patient Population:	Subjects aged 10-21 with Down syndrome and Obstructive Sleep Apnea with previous treatment of adenotonsillectomy.
Inclusion / Exclusion Criteria:	**Inclusion Criteria:** All subjects that participate in this study must meet the following criteria: 1. Children and young adults with Down syndrome 2. Age 10-21 years 3. Prior adenotonsillectomy 4. Moderate to severe OSA (AHI >10, AHI <50, no more than 25% AHI attributable to central events) based on prior in-lab PSG performed after adenotonsillectomy 5. Subjects must have either tracheotomy or be ineffectively treated with CPAP due to noncompliance, discomfort, un-desirable side effects, persistent symptoms despite compliance use, or refusal to use the device. 6. Children and their parents must be willing to have stimulation hardware permanently implanted, and be willing to participate in follow-up visits, postoperative PSG, and questionnaire completion. 7. Children's parents must complete a questionnaire confirming that their child is capable of communicating feelings of pain or discomfort. They must also confirm they are able to assess their child for adverse effects related to device implantation. 8. Children and their parents must be proficient in English. **Exclusion Criteria:** The presence of any of the following will exclude a potential subject from participation: 1. BMI>the 95th percentile for age 2. Any anatomic finding on physical exam or DISE that would compromise the performance of stimulation (e.g. concentric soft palate collapse) 3. Other medical conditions resulting in medical instability (e.g. congestive heart failure, recent open heart surgery, immunosuppression, or chronic lung disease or aspiration) 4. Presence of another medical condition requiring future magnetic resonance imaging (MRI) of the chest 5. Patients with another implantable device which could interact unintentionally with the Inspire system 6. Any contraindication for general anesthesia 7. Life expectancy < 12 months 8. Inability to communicate pain or discomfort to their caretaker/parent, based on parental or investigator assessment 9. History of bleeding or clotting disorders and those on blood

	thinning or NSAID medications for the week prior implantation surgery. Subjects will be asked to refrain from the use of NSAIDS for two weeks after the implantation or any revision surgeries. 10. Taking muscle relaxant medication 11. Female subjects who are pregnant or plan to become pregnant during the study period. 12. Subjects deemed unfit for participation by investigators or any other reason.
Objectives:	**Primary Objectives:** 1. Evaluate device related serious adverse events from implant to 12 month follow-up 2. Evaluate device-related adverse events from implant to 12 month follow-up **Secondary Objectives:** 1. Therapy efficacy measured by OSA-18 and ESS at 12 month follow-up 2. Therapy efficacy measured by AHI at 12 month follow-up 3. Objective mean weekly usage data obtained from the physician programmer at the 12 month visit
Investigational Intervention:	All enrolled patients will undergo device implantation surgery of the investigational device, device activation, and several follow-up visits.

Principal Investigator Signature Page

Protocol Title: A pilot study to evaluate safety and efficacy of the hypoglossal nerve stimulator in adolescents with Down syndrome and obstructive sleep apnea

Protocol #: 14-146H

Protocol Version Number/Date: Version 9.0; 05 July 2019

I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement.

_____
Name

_____
Signature

_____
Date

1 Introduction

1.1 Study Rationale

Obstructive sleep apnea (OSA) affects up to 1% of the general pediatric population and is associated with adverse behavior and quality of life, as well as long term cardiopulmonary system complications. Trisomy 21 (Down syndrome) is the most common chromosomal disorder, with an incidence of approximately 1 per 660-800 births. Patients with Down syndrome have a higher incidence of OSA than the general pediatric population, with rates of 30-60%, resulting in increased morbidity and decreased quality of life for affected individuals. In children, adenotonsillar hypertropy is often a contributing factor to OSA, and adenotonsillectomy is a first line treatment. Children with Down syndrome often undergo T&A for obstructive sleep apnea; however 30-50% will have persistent obstructive sleep patterns requiring continuous positive pressure airway support (CPAP) or tracheotomy. Persistent obstruction is attributed to anatomic and physiologic differences in this population, including reduced muscular tone, macroglossia, maxillary hypoplasia, and lingual tonsil hypertrophy. This pilot study is designed to determine if the Inspire® Upper Airway Simulation System, Model 3024 IPG (now Model 3028 IPG; see below), which has already been approved for use in adults with OSA, can be safely implanted and used in the treatment of adolescents and young adults with Down Syndrome.

The Inspire system was developed to treat moderate to severe OSA (15 ≤ Apnea Hypopnea - AHI ≤ 65) in adult patients who are not effectively treated by CPAP. The Inspire system is comprised of the following components:

- Inspire II Upper Airway Stimulator, Model 3024 (Implantable Pulse Generator, IPG) *and any subsequent iteration thereof that are approved under P130008 for the treatment of obstructive sleep apnea which are listed below and updated as needed via protocol modifications submitted to the FDA.* Note: Inspire Model 3028 IPG received FDA approval on May 5, 2017 and replaces Model 3024 IPG.
- Inspire Stimulation Lead, Model 4063 (stimulation lead)
- Inspire Sensing Lead, Model 4323 (sensing lead)
- External programmers used with the system are:
    - Inspire Programmer, Model 2740 (physician programmer)
    - Inspire Patient Programmer, Model 3032 (patient programmer)

1.2 Background

A global pivotal trial (the STAR trial) and three feasibility studies have been performed with the Inspire system. The first feasibility study (Inspire 1) implanted the Inspire I system in 8 subjects demonstrating the feasibility and safety of the approach.

Two additional feasibility clinical studies using the second generation Inspire system have verified the reliability of system components, and identified the specific inclusion and exclusion criteria in order for patients to obtain the maximum benefits from the Inspire system.

The STAR phase III pivotal trial demonstrated the safety, efficacy, and usability of the Inspire system. The study was conducted at 15 investigational sites in the United States and 7 investigational sites in Europe. The study followed 126 subjects implanted with the Inspire system. The study results met and exceeded all primary and secondary endpoints. Inspire therapy demonstrated statistically significant reduction of OSA severity, clinically meaningful improvement of quality of life, and with a safety profile well accepted by study subjects.

This protocol is the first known trial of children with Down syndrome being implanted with the Inspire system. Preliminary results were published for the first patient (1), the first 6 patients (2), and later for the first 20 implanted patients (3).

2 Objectives

2.1 Primary Objectives

1. Evaluate device-related serious adverse events from implant to 12 month follow-up
2. Evaluate device-related adverse events from implant to 12 month follow-up

2.2 Secondary Objectives

1. Efficacy of HGN stimulation as measured by OSA-18 and ESS at 12 month follow up
2. Efficacy of HGN stimulation as measured by AHI at 12 month follow-up
3. Objective mean weekly usage data obtained from the physician programmer at 12 month follow-up

3 Study Design

The study is a multi-center, prospective, single-arm study conducted under a common implant and follow-up protocol. Fifty adolescents and young adults (10-21 years of age) with Down syndrome with moderate to severe obstructive sleep apnea after adenotonsillectomy.

After providing informed consent, patients (with input from their parents/guardians as appropriate) will be screened according to the eligibility criteria below. Subjects will then undergo preoperative evaluation with an in-lab polysomnogram (PSG) (***if available, an in-lab PSG performed within 18 months prior to study consent may be used)***, evaluation by a pediatric otolaryngology surgeon, and drug induced sleep endoscopy (DISE) ***(If available, a DISE that was performed within 18 months of the study consent may be used)*** to ensure all inclusion and exclusion criteria are met.

Subjects meeting eligibility criteria will then undergo hypoglossal nerve implantation of the Inspire® Upper Airway Simulation System. Surgery will be performed by pediatric otolaryngologists who have completed a training program for the Inspire system.

Subjects will then adhere to a follow-up schedule. The device will be activated and settings titrated during an in-lab sleep study 1 month postoperatively. Quality of life surveys and device interrogation will be conducted at timed intervals. Subjects will then undergo in-lab polysomnography at 2 months, 6 months, and 12-months, and the device titrated as needed. All personnel adjusting device parameters will be trained in programming the Inspire system. For this pilot study, we will evaluate safety and efficacy over the first year after device implantation.

4 Patient Selection

4.1 Inclusion Criteria

All subjects that participate in this study must meet the following criteria:

1. Children and young adults with Down syndrome
2. Age 10-21 years
3. Prior adenotonsillectomy
4. Moderate to severe OSA (AHI >10, AHI <50, no more than 25% AHI attributable to central events) based on prior in-lab polysomnography performed after adenotonsillectomy
5. Subjects must have either tracheotomy or be ineffectively treated with CPAP due to noncompliance, discomfort, un-desirable side effects, persistent symptoms despite compliance use, or refusal to use the device.

6. Children and their parents must be willing to have stimulation hardware permanently implanted, and be willing to participate in follow-up visits, postoperative polysomnography, and questionnaire completion.
7. Children's parents must complete a questionnaire confirming that their child is capable of communicating feelings of pain or discomfort. They must also confirm they are able to assess their child for adverse effects related to device implantation.
8. Children and their parents must be proficient in English for this pilot study in order to ensure full disclosure during the consent process, as well as have the ability to communicate with all staff, at all times, regarding any questions about participation or concerns about this device. In further studies, we plan to expand study materials and resources in order to include patients who are non-English speaking. Given the small scale of this pilot study, we feel initial exclusion of non-English speaking individuals should not adversely affect applicability of our results to the general population, nor should it prevent all qualified patients from eventual access to device implantation.

4.2 Exclusion Criteria

The presence of any of the following will exclude a potential subject from participation:

1. BMI>the 95th percentile for age
2. Any anatomic finding on physical exam or drug induced sleep endoscopy (DISE) that would compromise the performance of stimulation (e.g. concentric soft palate collapse),
3. Other medical conditions resulting in medical instability (e.g. congestive heart failure, recent open heart surgery, immunosuppression, or chronic lung disease or aspiration)
4. Presence of another medical condition requiring future magnetic resonance imaging (MRI) of the chest
5. Patients with another implantable device which could interact unintentionally with the Inspire system
6. Any contraindication for general anesthesia
7. Life expectancy < 12 months
8. Inability to communicate pain or discomfort to their caretaker/parent, based on parental or investigator assessment
9. History of bleeding or clotting disorders and those on blood thinning or NSAID medications for the week prior implantation surgery. Subjects will be asked to refrain from the use of NSAIDS for two weeks after the implantation or any revision surgeries.
10. Taking muscle relaxant medication
11. Female subjects who are pregnant or plan to become pregnant during the study period. All female subjects aged 11 and up will undergo urine beta-HCG testing on the day of procedures requiring general anesthesia (DISE, implantation, and any other unanticipated surgical procedures related to implantation). Subjects who are positive will not undergo surgical implantation or procedures under general anesthesia.
12. Subjects deemed unfit for participation by investigators or any other reason.

4.3 Strategies for Recruitment and Retention

Up to forty-two (42) subjects will be recruited from the practices of participating investigators as well as referrals to these investigators; however, the study may stop after enrollment of only 40 subjects if some participants choose not to undergo surgery. Subjects who are deemed appropriate for the study (e.g. by answering screening questions and meeting general study criteria such as age) during their initial contact with the site investigator will be approached to participate and given information about the study by the site investigator and study staff. Subjects will be given the opportunity to ask any questions and if desired, the consent forms so they can review the study away from study staff. Subjects will also be given contact information for the study team should they have further questions once they leave the clinic or hospital.

Furthermore, if enrollment for a particular group does not seem adequate, then steps will be taken to promote increased enrollment of the under-represented group. Such steps include: 1) we will contact regional pediatric ENT clinics and post information in clinics that specifies that female or minority children with DS are especially desired; 2); we will reach out to local, state, regional, and national Down syndrome groups, and 3) an additional study site may be added.

5 Study Procedures

5.1 Schedule of Events

	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening / Baseline	Implant Surgery	Device Activation (1M post-op)	2M (5)	6M (5)	12M (5)
Eligibility	X					
Informed Consent	X (1)	X (2)				
Surgical Consultation	X					
Limited Physical Exam	X		X	X	X	X
Functional Tongue Exam	X	X	X	X	X	X
Medication Reconciliation	X		X	X	X	X
QOL (ESS, OSA-18)	X					X
In-Lab PSG	X (3)		X	X	X	X
DISE	X (3)					
Urine Pregnancy	X (6)					
Surgery		X				
Device Check			X	X	X	X
AE Review		X	X	X	X	X

(1) Informed Consent may be done in 2 stages if approved by the institution's local IRB. For patients who are considering participation but do not have the funds to travel to the study site for pre-screening, a remote consent may be conducted (if IRB approved) to allow for review of medical records for the purpose of screening for the study. Stage 2 will be in person consent for participation in the study. In person consent for participation in the study is required for all subjects.
(2) Separate surgical consent is obtained as part of standard of care based on institutional requirements.
(3) If In-lab PSG and DISE done as part of standard of care within 18 months of consent, these tests do not need to be repeated.
(4) 4-14 days post activation
(5) +/- 30 days
(6) Done for females age 11 and up prior to procedures done on study that require anesthesia

5.2 Assessments

5.2.1 Limited Physical Exam with Functional Tongue Exam

A limited physical examination will occur for each subject during study visit. This examination will be performed at Baseline, 1-, 2-, 6- and 12-month follow-ups.

At the Baseline visit, the examination will ensure that the subject is a good candidate to continue in the trial and receive the intended therapy. If any tongue dysfunction, atrophy, hypertrophy, fasciculations, problems swallowing or speaking are noted during the exam, they will be recorded.

At the post-implant follow-up visits, the exam will assess: appearance of surgical wound at the neck, facial nerve function, appearance of surgical wound on the chest, and tongue function. The tongue function exam

will assess any variation from the Baseline observations. Furthermore, the tongue exam is intended to detect any temporary or permanent damage to the hypoglossal nerve. For this reason, special attention is paid to muscle atrophy or hypertrophy, fasciculations, or limitations in tongue motion.

5.2.2 Surgical Consultation

Subjects will undergo a surgical consultation during pre-implant screening. The surgeon will perform a thorough head and neck examination, including laryngoscopy to evaluate the entire upper airway. A digital picture of the tongue and soft palate region may be taken (optional).

The subject will be disqualified for implant if any pronounced anatomical abnormalities exist (e.g., tonsil size of 3 or 4) that, in the Investigator's opinion, prevent effective use or assessment of the Inspire therapy. If a subject is excluded on the basis of Investigator opinion, the specific reason for exclusion will be documented.

5.2.3 Quality of Life Questionnaires

5.2.3.1 Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a validated, self-report instrument that rates a subject's tendency to fall asleep in eight common daily situations (4). The ESS Scale has been validated primarily in OSA. It is used to measure excessive daytime sleepiness, and is often utilized before and after the administration of treatment to document improvement of symptoms.

The ESS will be completed during the Baseline visit and 12-month follow-up.

5.2.3.2 Obstructive Sleep Apnea-18 (OSA-18)

The Obstructive Sleep Apnea-18 (OSA-18) is a survey given to caregivers to assess how sleep disordered breathing effects on the daily life of their children. It contains 18 questions related to 5 domains: 1) sleep disturbance, 2) physical suffering, 3) emotional distress, 4) day time problems, and 5) caregiver concerns. The survey has been shown to have good reliability and validity. The survey takes 5 to 10 minutes to complete.

A change score < 0.5 represents a trivial change, 0.5-0.9 indicates a small change, 1.0-1.4 demonstrate a moderate change, and ≥ 1.5 indicates a large change (5).

The OSA-18 will be completed at the Baseline visit and 12 month follow-up.

5.2.4 In-Lab Titration Sleep Study: Polysymnography (PSG)

Polysomnography will be conducted using standard techniques in the sleep laboratory. The AASM (American Association of Sleep Medicine) Manual of Scoring Sleep, 2007 (6) is used as a guideline for rules, terminology and technical specifications for the PSG study. Briefly, the following list of recordings will be collected.

1. Three channels of electroencephalogram
2. Chin electromyogram
3. Two channels of electrooculogram
4. A single bipolar modified Lead II for electrocardiogram
5. Chest and abdomen belts for respiratory effort measurement
6. One oronasal thermal sensor to detect the absence of airflow for apnea
7. One nasal pressure transducer for detection of airflow for hypopnea
8. One finger oximeter to continuously monitor arterial oxygen saturation
9. One position sensor to electronically determine position (supine, left, right, prone), or a means for documenting position
10. One leg electromyogram to record leg movements

All signals will be recorded on a digital PSG system and scored by the sleep lab. Prior to the PSG, the patients will fill out, or respond to, a Pre-PSG Interview that contains questions about recent behavior that may affect sleep during the PSG.

Note: If a PSG was completed within 18 months prior to study enrollment, study sites may use this PSG to determine eligibility for the study. At minimum, this PSG must follow AASM standards and must report AHI and > 25% of AHI attributable to central apnea as these are part of eligibility criteria.

5.2.5 Drug Induced Sleep Endoscopy (DISE)

Sleep endoscopies are routinely performed by ENT surgeons prior to sleep surgery to assess the location and extent of collapse of upper airway anatomical structures. Sleep endoscopy is typically performed in an operating room with the subject in the supine position. A digital video of the sleep endoscopy will be recorded. Continuous monitoring with electrocardiogram and oxygen saturation is performed. Induction of artificial sleep is achieved by an anaesthetist (or physician with equivalent training) by means of intravenous administration of propofol and/or midazolam. Anesthesia is titrated by targeting a level of light sedation such that the subject is arousable upon vocal stimulation.

Anatomical collapse is evaluated at the level of the palate, oropharynx, tongue base, and epiglottis. The degree of obstruction is characterized at each level as complete, partial, or none. The type of collapse is also characterized at each level as concentric, antero-posterior (A-P) or originating from the lateral wall. Subjects with complete concentric collapse at the level of the soft palate are not eligible for implant and exited from the study during pre-implant screening.

If a DISE is performed as a standard-of-care procedure within 18 months prior to consent, and results (documented in the medical history) clearly state that subject did not have complete concentric collapse at the level of the soft palate, then the implant may be scheduled.

A DISE must be performed after enrollment and before implant, if one did not occur within 18 months prior to signing consent. The DISE may be performed immediately prior to the implant (during the same procedure as the implant). This allowance is intended to prevent subjects from having to undergo an additional DISE procedure at centers where DISE is a standard assessment, when the DISE is likely to match a prior DISE result.

All video recordings of the DISE procedures will be uploaded electronically both to a secure hospital-hosted file transfer system and to a secure Inspire-hosted website. The video is then reviewed by a team of three specialist physicians, including the sponsor-investigator; at least two of the reviewing physicians must agree the subject is an appropriate candidate for surgery. The three doctors are Dr. Christopher Hartnick from Massachusetts Eye and Ear Infirmary, Dr. Ryan Soose from University of Pittsburgh Medical Center and Dr. Raj Dedhia from the University of Pennsylvania. If a DISE is to be performed just prior to surgery in order to decrease the number of times a subject is anesthetized, the physician reviewers will be alerted and available via phone to review the DISE in real-time. The decision of the physicians was previously documented via e-mail but as of version 9 of the protocol, a worksheet will be completed and signed by the sponsor-investigator; any additional documentation provided by the other physician reviewers will be included with the worksheet.

5.2.6 Device Check

Using the physician programmer, the general integrity of the system and subject use of the device will be verified. In addition, stimulation threshold testing may be performed where by the stimulation amplitude is adjusted..

During sensor testing, the physician programmer displays the respiratory pressure signal, as well as the timing of stimulation pulses. Adjustments can be made to the device sensing parameters (sensing thresholds and refractory periods) to synchronize stimulation with respiration. For example, if stimulation starts late, after the start of inspiration, the sensing parameters are made more sensitive to the start of inspiration. If the end of inspiration is not detected, then the sensing parameters detecting the end of inspiration are made more sensitive.

The device should be interrogated at the beginning of the subject's follow-up; and any programming changes that occur during the follow-up should be documented in the Device Check CRFs. Information will also be collected about the subject's use of the device since the last follow-up at each visit. Information concerning any difficulties in operating the system, and sudden changes in the effects of the system, will be documented.

Note: the Investigator will have received training on how to perform device programming, and will have the programmer technical manual available for reference. Therefore, detailed programming steps are not included in this protocol.

5.3 Study Visits

5.3.1 Screening / Baseline

Screening and Baseline activities may occur over several clinic visits, and may include information and/or tests that were performed locally within 18 months prior to signing consent. After consent is obtained (either in person consent to participate in the study or, if allowed by the local IRB, remote consent for screening), medical records including the PSG will be reviewed by the local PI and the DISE video will be reviewed by 3 person physician panel. If 2 of the 3 physicians agree the subjects is suitable, they will receive medical clearance for the surgery. The remainder of screening is to be completed by the local PI. Parents of eligible children interested in participation will sign a questionnaire affirming that their child is able to communicate pain or discomfort, as well as their ability to monitor their child for development of adverse side effects related to implantation.

At the baseline visit, consent to participate in the study will be obtained. After consent is obtained, a routine head and neck physical examination, including functional tongue exam will be performed. Parents will complete OSA-18 and ESS questionnaires prior to surgery.

5.3.2 Surgery

Prior to surgery, an institution specific surgical consent will also be completed by the parent and surgeon. On the day of implant before surgery the medication list will be reviewed and updated. Tongue movement and device function will be tested and documented at the time of implantation. A postoperative x-ray will be performed to document correct placement of the device. The device will remain off (turned "off," voltage set to = 0) until the activation and titration appointments scheduled approximately 1 month after surgery. The postoperative course and postoperative analgesics required will be documented.

A subject may undergo attempted implantation of the device, but the surgeon may be unsuccessful in placing the device. If one or both leads cannot be placed, the incision (s) will be closed, and the stimulator will not be implanted. The subject will return for a follow-up visit (usually within 14 days, but no greater than 30 days after attempted implantation). If no adverse event has occurred related to the surgery, the subject may be released from the study after the follow-up visit.

5.3.3 Standard of Care 1 Week Post-op Visit

As part of standard clinical care, subjects will be asked to see an ENT physician for a post-op wound check. For out of state subjects and families, this may be done at their local ENT. No data will be collected at this

visit. Subjects and their families will be instructed to call the study doctor if there are any issues noted at this visit or at any time during the study.

5.3.4 Device Activation and Initial Titration

At approximately 1 month (± 14 days) after implantation (or 1 month ± 14 days after any wound issues that arise have resolved), subjects will be seen at the office and on the same day be scheduled for an in-lab PSG. The surgeon will reassess the wound, perform a functional tongue exam, review and update the medication list, and check the device. The device will then be turned on and voltage adjusted to confirm that it is functioning. Voltage will be turned down to 0. The subject will then undergo overnight in-lab PSG and settings on the device will be titrated.

5.3.5 Follow-up Study Visits

5.3.5.1 2 Month Follow-Up Visit

Approximately 2 months (± 30 days) after implantation, the subject will be evaluated by the surgeon. A limited physical exam, including functional tongue exam, will be performed. Medication reconciliation will be performed. Any adverse events will be documented and submitted. The OSA-18 and ESS questionnaires will be administered. The device will be interrogated. The subject will then undergo in-lab PSG and if necessary, further titration. This in-lab PSG may occur within 2 weeks of the follow-up visit or as appointments are available at each site's sleep lab. However, all efforts should be made to keep the follow-up clinic visit and in-lab PSG as close as possible.

5.3.5.2 6 Month Follow-up Visit

Approximately 6 months (± 30 days) after implantation, the subject will be evaluated by the surgeon. A limited physical exam, including functional tongue exam, will be performed. Medication reconciliation will be performed. Any adverse events will be documented and submitted. The OSA-18 and ESS questionnaires will be administered. The device will be interrogated. The subject will then undergo in-lab PSG and if necessary, further titration. This in-lab PSG may occur within 2 weeks of the follow-up visit or as appointments are available at each site's sleep lab. However, all efforts should be made to keep the follow-up clinic visit and in-lab PSG as close as possible.

5.3.5.3 12 Month Follow-up Visit

Approximately 12 months (± 30 days) after implantation, the subject will be evaluated by the surgeon. A limited physical exam, including functional tongue exam, will be performed. Medication reconciliation will be performed. Any adverse events will be documented and submitted. The OSA-18 and ESS questionnaires will be administered. The device will be interrogated. Mean weekly usage data will be recorded, and a record will be kept of the physician programmer readout as supporting source documentation. The subject will then undergo in-lab PSG and if necessary, further titration. This in-lab PSG may occur within 2 weeks of the follow-up visit or as appointments are available at each site's sleep lab. However, all efforts should be made to keep the follow-up clinic visit and in-lab PSG as close as possible.

5.3.6 Unscheduled Visits

Subject visits to the center related to implantation outside of regularly scheduled visits as part of the study will be documented. If ineffective stimulation is noted, additional troubleshooting of the system may be required, or further investigations with in-lab PSG or DISE required. The investigators will refer to system manuals or seek assistance from Inspire representatives for support regarding troubleshooting procedures.

5.4 Concomitant Medications and Procedures

Subjects will continue their home medications during participation in the study, with the exception of NSAIDs or dietary supplements that increase the risk of bleeding in the immediate perioperative period (1 week before implantation and 2 weeks post-implantation). Subjects will receive standard anesthetics and postoperative pain medications. Medication logs will be reviewed, updated, and documented at each postoperative visit. General anesthesia in the Down syndrome population may cause increased risk of airway obstruction and bradycardia intraoperatively, as well as increases the risk of emergence agitation in the immediate postoperative period. This will be discussed with families during the consent process, as well as on the day of procedures when anesthesiology obtains anesthesia consent.

5.5 Participant Discontinuation / Withdrawal from the Study

5.5.1 Discontinuation of Device

Discontinuation of device use or choosing not to use the device does not mean discontinuation from the study, and any remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

5.5.2 Participant Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form, and are implanted, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

The DSMB may also determine whether participants should continue in the study as planned, proceed with modifications, or have their participation terminated. The justification to terminate a subject's participation may be due to the DSMB's analysis that there is a concern for the subject's safety or the subject's ability to comply with study requirements.

5.5.3 Device Failure, Revision, and Explant

5.5.3.1 System Revision

If the performance of the Inspire system remains unsatisfactory after troubleshooting, a replacement or adjustment to one or more components of the Inspire system (IPG, stimulation lead, or sensing lead) may be considered. Specific guidance on removal or adjustment of implanted components is contained in system manuals. The decision for replacement must be reviewed with the device manufacturer. Explanted system components must be returned to the device manufacturer. If the therapy is abandoned, device removal will be discussed with the subject as described in the following section.

5.5.3.2 System Explant

The system may be explanted at any time during the study. Subjects may request that their device be removed due to discomfort of components, infection, erosion, or subject may not respond to the therapy and elect removal.

If the device is removed, the following CRFs must be completed.

- Adverse Event Form
- Updates to Medication Log

5.5.3.3 System Explant Post-Op Check

Following removal of the device or components, the subject will be seen 1 week (4-14 days) after revision or removal to check the subjects' well-being and examine the wound post-operatively.

The following CRFs will be completed during the Post-Op check:

- Physical Exam
- Updates to Medication Log
- Adverse Event Form (if applicable)

5.5.3.4 Disposition of Device Following Study Withdrawal

Subjects who withdraw from the study will need to discuss with their physician the disposition of their implanted system. Upon withdrawal from the study, the subject may continue with the use of the therapy, and should consult with the physician regarding long-term management with the therapy.

Investigators should discuss expectations with subjects who withdraw from the study including:

- MRI imaging of the chest may NOT be performed when system components are implanted. However, MRI imaging of the head and extremities may be performed as needed according to specific parameters.
- Inform personal physicians, consulting physicians, or dentists that a stimulation system is implanted.
- Carry the Inspire Medical Systems patient ID card at all times.
- Consult the study physician or the device manufacturer if the following medical treatments are required: dental procedures requiring a drill, surgery with electrocautery, irradiation therapy, lithotripsy, RF-ablation, high output ultrasonic therapy, other implantable stimulation therapy, or defibrillation.

5.5.4 Participant Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return to the clinic within 3 months of their scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit bi-weekly for 3 months and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6 Study Device

The Inspire system was developed to treat moderate to severe OSA (15 ≤ AHI ≤ 65) in adult patients who are not effectively treated by CPAP. The Inspire system is comprised of the following components (Figure 1):

- Inspire II Upper Airway Stimulator, Model 3024 (Implantable Pulse Generator, IPG) and any subsequent iteration thereof that are approved under P130008 for the treatment of obstructive sleep apnea which are listed below and updated as needed via protocol modifications submitted to the FDA. Note: Inspire Model 3028 IPG received FDA approval on May 5, 2017 and replaces Model 3024 IPG.
- Inspire Stimulation Lead, Model 4063 (stimulation lead)
- Inspire Sensing Lead, Model 4323 (sensing lead)
- External programmers used with the system are:
    - Inspire Programmer, Model 2740 (physician programmer)
    - Inspire Patient Programmer, Model 3032 (patient programmer)

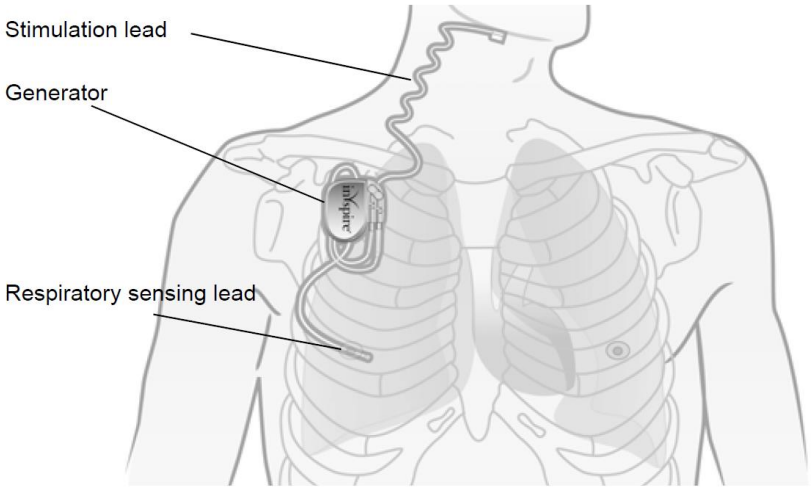


Figure 1. *Inspire system implanted components*

When the device is on, the Inspire system detects the patient's respiratory effort and maintains airway patency with mild stimulation of the hypoglossal nerve.

Device settings are stored in the IPG and configured by the physician using an external programmer.
The patient uses their Inspire sleep remote to turn the device on before they go to sleep and to turn therapy off when they wake up. The sleep remote also provides the ability to pause therapy and adjust stimulation amplitude within physician defined limits.

6.1 Device Components

The implanted components of the Inspire system consist of an Implantable Pulse Generator **(**IPG), a respiratory sensing lead, and a stimulation lead. All implanted Inspire system components are intended for single-use only.

6.1.1 Implantable Pulse Generator (IPG)

The IPG (Figure 2) contains the battery and electronics that deliver Inspire therapy and store the therapy settings.

Figure 2. *IPG*

The IPG has two 3.2 mm low-profile connector ports (Figure 3), which are compatible with the connectors on the stimulation lead and the respiratory sensing lead. After inserting the lead connectors into the IPG connector ports, the lead connectors are secured using the set screws next to the connector ports.

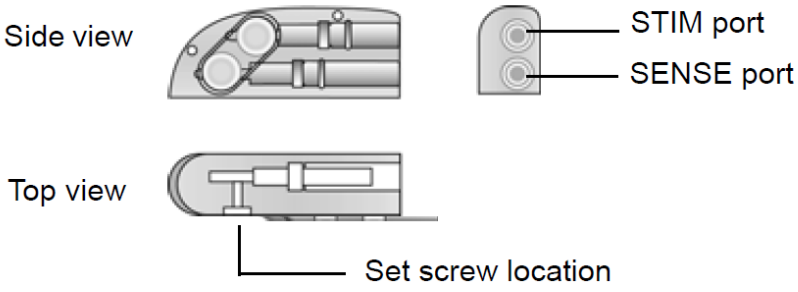


Figure 3. *IPG connector ports*

Only study investigators will perform device implantation surgery. In order to become certified to implant the Inspire device, all participating surgeons will need to complete a training program, including cadaveric dissections, offered by Inspire Medical Systems. This training program will also include modules on how the device is activated and programmed.

Sleep medicine physicians and involved technicians will also complete training on device programming and titration based upon sleep study results.

Using the physician programmer function on the device the general integrity of the system and subject use of the device can be verified. The device will be interrogated at the 2 month, 6 month and 12 month visits, as well as at any unplanned visits. Programming changes, difficulties operating the system, or any sudden changes in the system's effects will be documented in the subject's case file.

Parents will be instructed on how to use the programmer to turn the device on/off and change settings by certified staff during activation, follow-up appointments, and during sleep studies.

Any adverse events that occur during baseline or screening procedures will be documented on the Adverse Event Form and submitted for review.

Refer to the System Implant Manual as well as the Patient Programmer Manual for details about the device, implant training, and system use.

6.2 Acquisition and accountability

Each site will be authorized to begin enrolling subjects and order study devices once all appropriate regulatory documentation has been collected. The study devices will be ordered based on each site's study device accountability plan. The devices will not arrive labeled, as Inspire is shipping devices from their clinical stock. Each site must label the device "CAUTION – Investigation device. Limited by Federal (or United States) law to investigational use" and document that the device has been labeled appropriately.

Devices must be stored in a secure (locked) area at room temperature. Access should be limited to designated study staff only. Device accountability logs will be provided to the site. It is the site's responsibility to document the receipt (including maintain shipping logs), disposition of the product (per subject use, including serial number of device used, serial number of remaining devices, etc.), transfer (if applicable) and return of all unopened study devices. This information must also be provided to the sponsor-investigator for recordkeeping purposes.

6.3 Product Storage and Stability

Inspire Medical Systems sterilizes the IPG and leads with ethylene oxide (EtO) prior to shipment.

6.3.1 IPG

Inspect the IPG sterile package prior to opening. If the IPG package is damaged, the IPG may be damaged as well. Return a damaged package to Inspire Medical Systems. The IPG box includes a sterilization indicator. This indicator is green after the device has been sterilized. **Do not use the IPG if the indicator is red.**

See Table 1 for IPG Storage and Handling

Table 1. IPG Storage and Handling

Handling and Storage: Acceptable	**Unacceptable**
Store and transport IPG within the following environmental temperature limits: -35 °C (-31 °F) to +58 °C (+136 °F). A full or partial electrical reset condition may occur at temperatures below -18 °C (0 °F)	Do not implant the IPG if it has been dropped on a hard surface from a height of 30 cm (12 in) or greater
Resterilization	
The IPG cannot be resterilized. • IPGs cannot be resterilized. If the sterile package seal is broken, or if the packages are otherwise damaged, do not use. • Return the package to your local Inspire Medical Systems representative, see back cover for address.	

6.3.2 Leads

If the lead sterile package seal is broken or the package is otherwise damaged, return the package to Inspire Medical Systems. Leads cannot be resterilized.

See Table 2 for Leads Storage, Handling, and Resterilization.

Table 2. Lead Storage and Handling

Handling and Storage: Acceptable	Unacceptable
Store and transport leads within the following environmental temperature limits: -10 °C (14 °F) to +55 °C (131 °F). Only use sterile-gloved hands to handle the lead; rinse sterile surgical gloves in sterile water before handling the lead. Protect leads from materials that shed lint and dust. Exercise care and appropriate instrument selection when handling the stimulation lead cuff with a surgical instrument.	Do not implant a lead that was dropped Avoid excessive traction or sharp instruments Avoid severe bending, kinking, stretching, or handling with surgical instruments. Do not immerse a lead in mineral oil or silicone oil.
Resterilization	
Leads cannot be resterilized. • If the sterile package seal is broken, or if the packages are otherwise damaged, do not use. • Return the package to your local Inspire Medical Systems representative, see back cover of this manual for addresses.	

7 Risks and Benefits

7.1 Known Potential Risks

7.1.1 Risks of Screening Procedures

7.1.1.1 Risks of Drug-Induced Sleep Endoscopy (DISE)

- Nose bleeding
- Trauma to the upper airway
- Suspension of breathing episode
- Light-headedness
- Pain or irritation in the throat or nasal passage

7.1.1.2 Risks of PSG Studies

- Inability to sleep in the PSG lab
- Irritation or bleeding at external electrode sites
- Bruising or bleeding or soreness from external electrode removal
- Fatigue the next day, loss of productivity
- May lead to pain or sleeplessness

7.1.2 Risk of Implantation Surgery

The surgical scar will be approximately 2 inches long, just below the chin. Normally this scar blends in with normal creases in the neck and is not disfiguring. The electrodes and sensor should not be noticeable underneath the skin. The stimulator may cause a small lump underneath the skin below the collar bone.

A minority of OSA patients also have other neurological causes of sleep apnea, called "central sleep apnea". If improvement in the subject's OSA by the implanted nerve stimulator reveals this other type of apnea, additional treatment during and after his/her hospitalization may be necessary.

7.1.2.1 Surgical Related Risks

- Post-surgical pain or tenderness near incisions
- Post-surgical headache, fever, or dizziness
- Post-surgical throat soreness from intubation
- Post-surgical nausea or vomiting
- Post-surgical irritability, nervousness, confusion
- Post-surgical sleep problems like insomnia or sleepiness
- Post-surgical constipation
- Post-surgical mild to moderate swelling, oozing, and/or bruising around the surgical incisions,
- Post-surgical back pain due to lying on the table during the procedure
- Depending on geography, standard uncomplicated post-implant hospitalization may be up to 36 hours.
- Damage to blood vessels (e.g. erosion) in the vicinity of implant
- Allergic and/or rejection response to the implanted materials
- Excessive bleeding
- Infection
- Trauma (e.g. perforation or dissection) or damage to arteries and veins
- Local irritation, infection, seroma (pocket of clear fluid under the skin, hematoma (blood outside the blood vessels), erosion, swelling
- Irritation or damage to nerves near the implant
- Persistent pain at the implant site
- Nerve trauma Pain, numbness or inflammation in the mouth, neck
- Hypoglossal nerve trauma or damage
- Strange sense of touch or burning sensation on the tongue or neck (dysesthesia)
- Procedure related deterioration of pre-existing medical condition
- Tongue movement restrictions
- Blood thinning medications may result in complications such as excessive bleeding, clotting, or hematomas
- Tongue may get larger (hypertrophy) or smaller (atrophy)
- Airway constriction or obstruction
- Tongue muscle twitches (Fasciculations)
- Air in the chest cavity (pneumothorax)
- Problems with swallowing or speaking
- Damage to the lung or membrane that surrounds the lung (pleura)
- Muscle stimulation of floor of mouth musculature
- Death Pneumothorax

7.1.2.2 Risks of Anesthesia

Drug induced sleep endoscopy, surgical implantation, battery replacement, electrode repositioning and device implantation will be performed under anesthesia. General anesthesia can result in airway obstruction, temporary changes in heart-rate and oxygen level, and changes in behavior as medications wear off. These risks are increased in subjects with Down syndrome.

7.1.2.3 Device Complications/Malfunctions

- Migration or traction of pulse generator or leads
- Elevated stimulation threshold
- Lead dislodgement
- Failure to stimulate
- Lead damage and/or failure
- Implantable Pulse Generator failure
- Premature battery failure
- Failure of respiratory sensing
- Breakage or misuse of surgical tools
- Misuse of the subject programmer may result in ineffective function
- Spontaneous stimulation and sensing threshold changes
- Therapy may irritate a subject, wake them, or prevent them from sleeping
- MRI can induce currents on implantable components, potentially causing tissue damage and tongue dysfunction
- MRI may cause damage to the device
- Should your child become pregnant, there may be unknown risks to the embryo or fetus
- There may be risks that are not currently known at this time
- Implanted parts may need to be surgically moved or removed

7.1.2.4 Potential Need for More Surgery

Battery replacement: The implanted device is powered by a battery that has an expected lifespan of 5-8 years. The lifespan of the battery will vary based on the stimulation parameters that the investigator programs into the subject's device. Although unlikely, the battery may deplete sooner than expected. Battery replacement is performed through a small incision at the device implant site below the subject's collar bone under local anesthesia, where a numbing medication is injected into the tissue over the implant.

Repositioning or replacement of stimulation or sensing leads: If one of the implanted leads moves, the investigator may need to perform another surgery to reposition or replace the lead in order for the subject to continue to use the device. Risks related to another surgery are described in the potential risk section (table), as well as sections on considerations for implanted device removal and potential risks associated with implanted device removal.

7.1.3 Pregnancy Risks

A female subjects may not take part in the study if she is pregnant or has plans to become pregnant during the study period due to procedures that require general anesthesia. All female subjects aged 11 and up will undergo urine beta-HCG testing on the day of procedures requiring general anesthesia (DISE, implantation, and any other unanticipated surgical procedures related to implantation). Subjects who are positive will not undergo surgical implantation or procedures under general anesthesia.

7.1.4 Psychosocial (non-medical) Risks

Subjects may experience distress regarding discomfort from the surgery or device.

7.1.5 Considerations for Future Medical Care

Strong magnetic fields generated by magnetic resonance imaging (MRI) scanners may move the stimulation device, leads, or cause excessive stimulation**. After the device is implanted, the subject will not be able**

to have an MRI scan of the chest, but will able to get MRI imaging of the head and extremities ONLY according to specific parameters. Other available testing methods, such as CT scan, ultrasound, and X-ray, which will not interfere with the implanted device should be considered. If an MRI scan is needed of the chest, the Inspire® system must be removed surgically.

Precautions must be taken around theft and security detectors (such as those found in museums, retail stores, courthouses, and airports). The magnetic fields created by this equipment could cause the implanted device to stimulate the subject's tongue. In rare cases, they could also reset the device to zero volts. If this happened, it would become clear the next time the subject tried to use the device. When the remote is positioned above the subject, it will beep if the device is working properly; it will not beep if the device has been reset to zero volts. Should the device be reset, the subject will need to see the doctor to have the device reprogrammed.
During the course of the subject's life, additional implantable devices such as cardiac defibrillators or pacemakers may need to be placed. The nerve stimulator might interfere with functioning of these devices. Therefore, it is important that any doctor taking care of the subject know about the nerve stimulator that is implanted. The treating doctor should contact the investigator of this trial prior to any procedure to ensure that the subject's implanted device remains safe.

A wallet card and laminated letter will be provided to subjects identifying them as having this implant. Written instructions will be provided to families detailing important information dentists and other surgeons should know when providing medical care to the subject.

7.2 Known Potential Benefits
Based on previous studies with the adult population, it is expected that the device will improve sleep in a majority of the enrolled subjects. Furthermore, subjects in this study may benefit from additional contact with clinicians and medical testing that could lead to early detection of and or advanced treatment of a medical condition that was not previously diagnosed.

8 Data Safety and Monitoring

8.1 Data Safety and Monitoring Board
The Data and Safety Monitoring Board (DSMB) will serve as the independent data and safety monitoring board for this study. The DSMB will meet regularly as laid out in the DSMB charter to review progress of the study and will be available for emergent meetings if serious or unanticipated adverse events occur. The serious adverse events and responses will be reviewed by the DSMB.

8.2 Research monitor
The chair of the DSMB will also serve as the Research Monitor. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or the Data Safety and Monitoring Board (DSMB).

8.3 Regular Site Monitoring
An external monitor will be contracted by the sponsor-investigator to do on site monitoring. This monitoring will be done at regular intervals as outlined by the Monitoring Plan to ensure study compliance with the protocol and all applicable laws, regulations, and guidelines.

8.4 Adverse Event Monitoring and Reporting

All adverse events (AEs) will be documented in a timely manner throughout the clinical trial and reported in the database. All events will be reported to the PI, FDA, and DSMB. The sponsor-investigator has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations. All adverse events and adverse device effects will be reported in all geographies. Reportable adverse events will be monitored prospectively from enrollment (consent) to the end of the follow-up period. **For the purposes of this study, reportable AEs include all events meeting the definition of "serious" as well as *any* events possibly related to the study procedures, study device, therapy or required testing. See Figure 4 (Classification of Adverse Events) to determine whether in AE is reportable.**

8.4.1 AE Definitions for Investigator Classification

Investigators are responsible for categorizing adverse events according to their seriousness and relatedness (e.g., to the surgical procedure, to the Inspire system, etc.). The Sponsor will then review all reported adverse events for completeness, and ask for clarification or additional information if necessary. The definitions for classifications are included below and on the provided adverse event log. Those events that do not meet the criteria for Serious Adverse Event are considered non-serious.

8.4.1.1 Adverse Event

An Adverse Event (AE) is any undesirable subject event that occurs during the course of the study, from consent through exit. For the purpose of the study, reportable AEs include all events meeting the definition of "serious" as well as any events possibly related to the study procedure, study device, therapy or required study testing.

8.4.1.2 Serious Adverse Event

Serious AEs will be identified as such on the AE CRF and defined as any adverse experience that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not meet one of the above definitions could be considered SAEs if they jeopardize the health of the subject or require surgical intervention to prevent one of the outcomes listed in the definition above. Serious adverse events may or may not be related to the procedure, system or therapy.

8.4.1.3 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any event on the subjects' health, safety, or welfare not previously identified in nature, severity, or degree of incidence in the investigator's brochure and investigational plan. A serious device-related AE which is not identified as a potential complication in the labelling, and is unanticipated, adverse, and a consequence of the use of the Inspire system, must be reported to the sponsor as soon as possible, but in no case greater than five working days from the first knowledge of the occurrence. The sponsor-investigator will coordinate with the site Investigator on the submission of specific clinical documentation appropriate to the UADE encountered. In addition, written notice must also be supplied to the sponsor and reviewing IRB within 10 working days.

Any unanticipated adverse effects will be investigated immediately and if unreasonable risk to the patient population is not preventable, the study will be terminated and all regulating authorities and participating investigators will be notified. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later the 15 working days after the Sponsor first received notice of the effect. A terminated investigation may not be resumed without IRB approval.

8.4.2 Adverse Event Reporting

All procedure and device related events will be collected during this study. In addition, all adverse events meeting the definition of 'serious' (Section 10.12) are required to be reported. All reportable adverse events are to be recorded on the AE CRF at the time of the occurrence(s) or at the time the Investigator becomes aware of the occurrence(s). Additional information, such as procedural notes, operative notes, or a signed clinical summary may be required as supporting documentation for the reported AE. All identifying information should be removed from these supportive documents and the subject's study number should be used.

All adverse events must also be described by: duration (onset and resolution dates); severity; relationship to the procedure, device or therapy; action taken to resolve the event; the outcome of the event and if it meets the definition of 'serious'. In addition a code will be assigned to the event based on type of relationship determined. Relationship categories and codes are described below. All adverse events should be followed until the adverse event has been resolved, the subject has reached maximum medical improvement with no further actions to be taken, the subject exits the study, or until study closure, whichever occurs first.

The timeframe for reporting of serious or unexpected AE's to the Sponsor and governing IRB is presented in the table below (Table 3):

Table 3: Reporting requirements and Timeframe for SAEs and UADEs

Type of AE	Reporting Timeframe
SAE	Notify sponsor-investigator as soon as possible, with full report no later than 10 working days of occurrence or sites knowledge
UADE	Notify sponsor-investigator as soon as possible, with full report no later than 10 working days of occurrence or sites knowledge
Death	Notify sponsor-investigator within 24 hours

8.4.2.1 Relationship

Investigators are also responsible to categorize adverse events according to their relatedness. The definitions for relatedness classifications are included below.

8.4.2.1.1 Surgery Related

A surgical related adverse event is any adverse event that is related to or possibly related to the surgical procedure to implant the device. These events typically occur within 30 days of surgery. Examples include significant bleeding during surgery, infection, acute tongue weakness.

Any normal and expected postoperative complaints or symptoms are **not** required to be reported, unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary postoperative care. Expected postoperative care outcomes include: headache, incisional pain, nausea, vomiting, low grade fever, oozing at dressing, dizziness, irritability, nervousness, temporary sleep problems like insomnia or sleepiness, constipation, confusion and similar

events, tenderness, throat soreness secondary to intubation, or mild to moderate swelling and/or bruising around the implant site, back pain due to lying on the table during the procedure.

8.4.2.1.2 Device Related

A device related adverse event is any adverse event that is related or possibly related to use of the device. Examples include device-related injection, undesirable change in stimulation (e.g. jolting or shocking), chronic or intermittent tongue soreness, discomfort, or intense stimulation. Acute events that occur during a device check that subside once acceptable parameters are selected are not reportable.

8.4.2.1.3 Other Protocol Testing or Evaluation Related

Other procedures required as part of the study protocol but not associated with an Inspire system implant or Inspire device, that result in an AE. Examples include: sore neck from in-lab PSG; nausea from anesthesia during DISE, etc.

8.4.2.2 Degree of Intensity / Severity

In addition, investigators will categorize the intensity / severity of all AEs CRF as:

Mild: Awareness of event, but easily tolerated
Moderate: Discomfort enough to cause interference with usual activity
Severe: Inability to carry out usual activity

This determination is distinct and separate from the determination of whether or not an event is an adverse event (AE) or a serious adverse event (SAE).

8.4.3 Anticipated Adverse Device-Related Events

Anticipated device related AEs (medical change from baseline), which may possibly be seen during this study, include the following presented in Table 4 (below), as reported in the PMA submission for 126 implanted subjects.

Table 4: Anticipated Adverse Device-Related Events

Adverse Event	Total Number of Events	% of Subjects (n) N=126
Discomfort due to electrical stimulation	66	33% (42)
Temporary Tongue weakness or deviation	35	18% (23)
Tongue abrasion	23	16% (20)
Mechanical pain associated with presence of device	6	5% (6)
Infection (mild or moderate)	1	1% (1)

8.4.4 Technical Observation/Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety, or performance of an investigational device shall be documented throughout the investigation. Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence shall be reported including if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate.

User Error: An instance where an act or omission of an act results in a different medical device response than intended by the manufacturer or expected by the user is considered a 'user error'. This includes slips,

lapses and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

8.4.5 Subject Death

A subject death during the study must be reported to Sponsor as soon as possible. Notification of death must include a detailed narrative that provides detailed information describing the circumstances surrounding the death and is signed by the Principal Investigator or authorized co-Investigator. The death letter should include the following information:

- Date and time of death
- Place death occurred
- Immediate cause of death
- The relatedness of the death to the Inspire system, surgical procedure, neurostimulation, clinical investigation, or subject condition.
- Whether or not the death was witnessed
- Device status and/or activity at the time of death
- Any other circumstances surrounding the death

The PI or co-Investigator must sign and date the letter. If information listed above that is unavailable or unknown must be specified in the death letter. Also the following documentation should be obtained:

- If the subject expired in the hospital, a copy of the medical records for that admission (e.g., H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

The study exit CRF will be completed and any open events will be formally closed in the database (outcome: death). Whenever possible, the pulse generator should be interrogated. Study devices and related Sponsor system components (e.g., leads) should be removed intact and returned promptly to Sponsor for analysis.

9 Statistical Considerations

9.1 Primary endpoint(s) or outcome measure(s)

- The primary endpoint of this pilot study is to assess the safety of hypoglossal nerve stimulator placement for the treatment of obstructive sleep apnea in adolescents with Down Syndrome.
- Safety of implantation will be monitored throughout the perioperative period and unanticipated and anticipated adverse device related events will be recorded.

9.2 Secondary endpoints or outcome measure(s)

- The secondary endpoint of this study is to assess the efficacy of hypoglossal nerve stimulator placement in this patient population.
- Effectiveness in the treatment of obstructive sleep apnea will be measured using standard in-lab PSG measures, including oxygen level, partial and complete airway obstruction, and arousals. Improvement will be defined as a 50% or more decrease in AHI. This will be measured prior to implantation, and compared to post-implantation values at 2 months, 6 months, and 12 months.
- Compliance will be assessed by objective data gathered by the device, which will be downloaded using the physician programming function at follow-up visits.

- Quality of life improvements will also be measured using the OSA-18 questionnaire and Epsworth Sleepiness Scale. Assessments will be performed preoperatively then at 2 months, 6 months, and 12 months.

9.3 Sample Size Determination

This is a pilot study designed to assess if the hypoglossal nerve stimulator can be safely implanted and utilized by adolescents with Down syndrome. Up to forty-two (42) adolescents and young adults will undergo implantation for this study. If implantation can be safely performed in this population, further studies will be designed and powered to assess for significant changes on PSG and quality of life with device usage.

9.4 Analysis Population

The pilot study population is designed as part of a preliminary efficacy study and will be utilized in the statistical evaluation of study endpoints.

9.5 Effectiveness Analysis (if applicable)

- Pre and post-implantation quality of life scores and polysomnogram values will be used to assess the effectiveness of hypoglossal nerve implantation in the treatment of obstructive sleep apnea in adolescents with Down Syndrome.
- Any deviations from the previously described statistical plan will be described and justified in a protocol amendment and/or in the final report submitted to this application.

9.6 Safety Analysis

Anticipated and unanticipated adverse events related to device implantation will be recorded prospectively, examined and reported.

10 Ethical Considerations

10.1 Review by an Institutional Review Board

Prior to initiation of the research described in this document, it will be reviewed by an institutional review board as required by 21 CFR 56.

10.2 Informed Consent

Prior to enrolling any potential subject or performing any non-standard of care study procedures, all potential subjects will be consented as required by 21 CFR 50.

10.2.1 Inclusion of Minors

As this study will enroll minors between the ages of 12 and 17, care will be taken to ensure the rights of this subject population. Both parents/guardians of the potential subject will be consented unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.. Of note, it is possible that one parent may not be reasonably available due to inability to travel to a study site based on financial restrictions or other logistical concerns such as childcare for other children, job requirements, etc. In such cases, both parents will discuss the study with the local PI via telephone and those discussions will be documented, along with the reason that one parent will not be available to sign consent in person on the day of consent.

Additionally, the underage subject themselves will also be assented. Written assent is preferred, but verbal assent will be obtained and documented in cases where the subject's maturity and/or ability make obtaining written consent infeasible. If the underage subject turns 18 during the course of the study, and they are capable of providing consent for themselves, they will be re-consented, as they can determine for themselves if they wish to continue to participate in the study. If an underage subject turns 18 and is not capable of

providing consent for themselves, the previously obtained parental permission and assent will remain effective and this determination will be documented in the medical record and study record.

10.2.2 Inclusion of Persons not Competent to Consent

As this study will enroll subjects with Down syndrome up to age 21, care will be taken to ensure the rights of adult subjects, 18 and older, who are not competent to consent. If an adult subject is deemed incapable of providing consent, two parent/guardian consent and subject assent will be obtained as with pediatric subjects on this trial.

10.2.3 Non-English Speaking Subjects

As this is a pilot study with a significant risk device, all subjects and their parents must be able to communicate questions and concerns to the study staff at all times. All subjects and all parents must be proficient in English for this to occur. In further studies, we plan to expand study materials and resources in order to include patients who are non-English speaking. Given the small scale of this pilot study, we feel initial exclusion of non-English speaking individuals should not adversely affect applicability of our results to the general population, nor should it prevent all qualified patients from eventual access to device implantation.

10.3 Statement of Compliance

This study will be performed in compliance with all applicable federal, state, and local regulations and requirements for the protection of human subjects in a clinical trial.

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