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Multicentre study conducted across centres in the USA, Europe and Australia to assess the safety and effectiveness of a bilateral hypoglossal nerve stimulation system for the treatment of obstructive sleep apnoea in adults: a protocol for a pivotal, multicentre, open-label, single-arm study

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ABSTRACT

Introduction Obstructive sleep apnoea (OSA) is characterised by blood oxygen desaturations and sleep disruptions manifesting undesirable consequences. Existing treatments including oral appliances, positive airway pressure (PAP) therapy and surgically altering the anatomy of the pharynx have drawbacks including poor long-term adherence or often involving irreversible, invasive procedures. Bilateral hypoglossal nerve stimulation (HNS_{BL}) is a new treatment for managing OSA, and this study is intended to determine whether an HNS_{BL} system is a safe and effective treatment option for adults with OSA.

Methods and analysis This is a pivotal, multicentre, prospective, single-arm study of HNS_{BL} in PAP-intolerant adults with moderate to severe OSA. The device is activated 2 months after implantation with stimulation settings optimised before the final 12-month sleep study. At 12 months, the two coprimary effectiveness endpoints are the percentage of responders based on reduction in the Apnoea-Hypoponea Index, with hypopnoeas associated with 4% oxyhaemoglobin desaturation, and the Oxygen Desaturation Index, using drops in oxygen concentration >4% from baseline (ODI4). Secondary effectiveness endpoints include mean changes in quality-of-life assessments (daytime sleepiness and its effect on activities of daily living, OSA-specific quality of life, daytime sleepiness), levels of intermittent hypoxia, change in hypoxaemic burden and OSA severity.

Ethics and dissemination The Food and Drug Administration, Advarra Institutional Review Board (IRB), University of Tennessee HSC IRB, University of Pennsylvania IRB, Weill Cornell Medicine IRB, Medical College of Wisconsin/Froedert Hospital, Human Research Protections Programme Vanderbilt University, St. Vincent's Hospital Melbourne Human Research Ethics Committee, Ethisch Comite Universitair Ziekenhuis Antwerpen and Technische Universitat Munchen reviewed and approved this protocol. Study results will be disseminated through journal publications, updates to ClinicalTrials.gov and the Nyxoah website, and presentations at meetings and conferences.

Trial registration number NCT03868618.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Enrolling patients across various treatment centres will lead to more generalisable results due to the inclusion of a diverse patient population.
⇒ Data collection procedures are defined prospectively, allowing for precise and systematic tracking of outcomes that can lead to more accurate and reliable data.
⇒ The single-arm design of the study avoids substantial recruitment and ethical challenges that exist when attempting to randomise patients to a surgical therapy.
⇒ The lack of a comparative or control group will limit the ability to directly evaluate HNS_{BL} in comparison to other therapeutic strategies.
⇒ The probability of selection bias is higher in this single-arm study as no randomisation procedures are used.

INTRODUCTION

Obstructive sleep apnoea (OSA) is characterised by recurrent episodes of partial

(hypopnoea) or complete (apnoea) obstructions of the upper airway.[1–3] The disturbances in respiratory airflow result in blood oxygen desaturations and sleep fragmentation that are associated with daytime sleepiness and multiple other comorbidities including hypertension, depression and stroke.[4] Positive airway pressure (PAP) therapy is the first-line treatment for moderate to severe OSA patients.[5] Although PAP is highly effective, patient acceptance and adherence to therapy are suboptimal.[6 7] Surgical treatments to reconstruct the upper airway are available for OSA; however, surgical procedures are generally considered less effective than PAP, and the morbidity associated with these procedures is often unacceptable to patients.[8]

Unilateral hypoglossal nerve stimulation was approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe OSA in 2014.[9] The system achieves stimulation using three implanted components: a pulse generator inferior to the clavicle, a tunnelled respiratory sensing lead placed between the external and internal intercostal muscles, and a tunnelled stimulation lead placed over the medial branches of the hypoglossal nerve. The 12-month pivotal trial results demonstrated improvements in Apnoea-Hypopnoea Index (AHI) and oxygen desaturation index (ODI) that remained stable at 36 months and 60 months.[10 11] Patient-reported outcomes were improved while serious adverse events (SAEs) were reported in 8 of 126 participants (6%) during this follow-up period. Although PAP, surgery and unilateral hypoglossal stimulation demonstrate effectiveness in improving OSA outcomes,[8 10 12] they are also associated with various drawbacks.[10 13]

Bilateral hypoglossal nerve stimulation (HNS_{BL}) is another potential treatment for OSA, and the current system consists of single component implanted through a single incision used in combination with an external activation chip (AC) that delivers radiofrequency energy via a disposable patch. The results from previous clinical testing of HNS_{BL} in patients with OSA have been positive, supporting the conduct of this pivotal study. The BLAST OSA feasibility study (NCT03048604) in a smaller cohort of 27 participants showed HNS_{BL} reduced OSA severity and improved participants' quality of life with no device-related SAEs at 6 months postimplant.[14] The current pivotal study is designed to assess the effectiveness endpoints in a larger pool of participants for an extended period of time and is intended to determine whether the HNS_{BL} system is a safe and effective treatment option for select PAP-intolerant adults with moderate to severe OSA.

METHODS

Study design

The Dual-sided Hypoglossal neRvE stimulAtion for the treatMent of Obstructive Sleep Apnea (DREAM) study is a pivotal, multicentre, prospective, single-arm study to evaluate the safety and effectiveness of HNS_{BL} for reducing the severity of moderate to severe OSA over a period of 12 months after surgical implant. This study is being conducted at academic and private practice sites (details can be found at https://clinicaltrials.gov/study/NCT03868618). The following information is correct as of V.7.0 of the protocol, dated 1 July 2022.

Patient and Public Involvement

The development of this study protocol did not involve patients or members of the public.

Study sample

It is anticipated that 750 participants need to be screened to achieve 115 evaluable study participants, as detailed below. Written informed consent is obtained from all enrolled participants before any study procedures are conducted. The master participant informed consent form can be found in online supplemental materials. Participants are recruited from the regular patient population of participating clinical sites and via print and social media advertisements. Participants are selected on the basis of a priori inclusion and exclusion criteria for this study (box 1), which were developed in collaboration with the US FDA using data from a prior feasibility study.[14] Each participant is followed for safety and effectiveness for 12 months postsurgery and will be asked to return for in-person visits biannually for up to 5 years postsurgery.

Assuming 80% statistical power, a 15% rate of non-evaluable implanted patients, and using a one-sided 2.5% level of significance and a one-sample exact binomial test, a sample of 115 eligible participants is sufficient to demonstrate whether the percentage of responders at month 12, based on AHI4 and ODI4, is higher than the prespecified performance goal of 50% for both coprimary effectiveness endpoints. This result assumes that the estimated percentages of responders will be 65% and 64% based on AHI4 and ODI4, respectively.

Intervention

As part of the eligibility assessment, an independent core lab evaluates locally completed drug-induced sleep endoscopy (DISE) recordings to exclude participants with complete concentric collapse of the soft palate. Following screening procedures and baseline polysomnography (PSG), the Genio (Nyxoah SA, Mont-Saint-Guibert, Belgium) implantable stimulator (IS) is implanted by a trained and certified surgeon via an incision made over the submental triangle (figure 1). The implant is placed over the genioglossus muscles with the electrodes proximate to the left and right medial branches of the hypoglossal nerve, and an external stimulator is used to power the IS and verify optimal implant placement and proper tongue protrusion. The implant is then secured in place using sutures with the antenna centred over the midline of the genioglossus muscle.

Based on prior trial experience with HNS_{BL},[14] the device is activated approximately 2 months after surgical implantation and the participant receives training in its use. Participants are instructed to use the system nightly,

Box 1 Study inclusion and exclusion criteria

Inclusion criteria

1. Age from 22 to 75 years (inclusive). Participant cannot be under guardianship, under curatorship or under judicial protection.
2. Body mass index ≤32 kg/m^2.
3. Cricomental space positive (≥0 cm). The cricomental space is the distance between the neck and the bisection of a line from the chin to the cricoid membrane when the head is in a neutral position.
4. Has either not tolerated, has failed or refused positive airway pressure (PAP) treatment.
5. Moderate to severe obstructive sleep apnoea (OSA) (15≤Apnoea-Hypopnoea Index, with hypopnoeas associated with 4% oxyhaemoglobin desaturation (AHI4)≤65 where combined central and mixed AHI<25% of the total AHI) based on a screening polysomnography (PSG).
6. Non-supine AHI>10 events on the screening PSG or participant has either not tolerated, has failed or refused positional therapy.
7. Written informed consent obtained from the participant prior to performing any study specific procedure.
8. Willing and capable to comply with all study requirements, including specific lifestyle considerations, performing all follow-up visits and sleep studies, evaluation procedures and questionnaires for the whole duration of the trial.
9. Willing to consent to long-term follow-up of 5 years postsurgery.

Exclusion criteria

1. Inadequately treated sleep disorders other than OSA that would confound functional sleep assessment:
   a. Severe chronic insomnia.
   b. Insufficient sleep syndrome (<6 hours sleep per night).
   c. Narcolepsy.
   d. Restless legs syndrome.
   e. Rapid Eye Movement (REM) behaviour disorder.
   f. Others deemed sufficient disorders that would confound functional sleep assessment in the judgement of the investigator.
2. Night shift worker is defined as individual working between the hours of 22:00 and 7:00 hours at least three nights per working week.
3. Taking medications that in the opinion of the investigator may alter consciousness, the pattern of respiration or sleep architecture.
4. Major anatomical or functional abnormalities that would impair the ability of the Genio System to treat OSA:
   a. Craniofacial abnormalities narrowing the airway or the implantation site.
   b. Palatine tonsil size 3+ or 4+ by the Brodsky classification.
   c. Fixed upper airway obstructions (tumour, polyps, nasal obstruction).
   d. Congenital malformations in the airway.
   e. Hypoglossal nerve palsy (bilateral limited tongue movement or unilateral unintended tongue deviation during protrusion).
   f. Existing swallowing difficulty as measured by a score of ≥3 on the Eating Assessment Tool (EAT)-10 questionnaire.
   g. Others deemed sufficient to impair the ability of the Genio System to treat OSA in the judgement of the investigator.
5. Significant comorbidities that contraindicate surgery or general anaesthesia:
   a. Revised Cardiac Risk Index Class III or IV.
   b. Persistent uncontrolled hypertension (defined as systolic pressure 160 mm Hg or a diastolic pressure of 120 mm Hg) despite medications.
   c. Coagulopathy or required anticoagulant medications (such as warfarin, clopidogrel (Plavix) or similar; prophylactic aspirin not exclusionary) that cannot be safely stopped in the perioperative period.
   d. Degenerative neurological disorder (ie, Parkinson's disease, Alzheimer's disease).
   e. Acute illness or infection.
   f. Diagnosed psychiatric disease (eg, psychotic illness, uncontrolled major depression or acute anxiety attacks) that prevents participant compliance with the requirements of the investigational study testing.
   g. Substance or alcohol abuse history within the previous 3 years. Alcohol and substance abuse are defined as follows:
      1. Alcohol: no days with less than three or four standard drinks for women and men, respectively.
      2. Substance: the use of any substance in an amount unapproved by the investigator or considered illegal. The drugs most commonly abused include cocaine, marijuana, heroin (or substitution treatment), prescription drugs (especially painkillers), methamphetamines and various other illegal substances.
   h. Life expectancy less than the primary endpoint study period (12 months postsurgery).
   i. Any other chronic medical illness or condition that contraindicates a surgical procedure or general anaesthesia in the judgement of the investigator.
6. Prior surgery or treatments that could compromise the effectiveness of the Genio System:
   a. Airway cancer surgery or radiation.
   b. Mandible or maxilla surgery in the previous 5 years (not counting dental treatments).
   c. Other upper airway surgery to remove obstructions related to OSA in the previous 3 months (eg, uvulopalatopharyngoplasty, tonsillectomy and nasal airway surgery).
   d. Prior hypoglossal nerve stimulation device implantation.
7. Has an Active Implantable Medical Device even if the device can be temporarily turned off.
8. Participation in another clinical study with an active treatment arm that could confound the results of the Dual-sided Hypoglossal neRvE stimulAtion for the treatMent of Obstructive Sleep Apnea study.
9. Plan to become pregnant, currently pregnant or breastfeeding during the study period.

and after a period of acclimation, the stimulation level of the device is optimised over several visits based on observations while awake and asleep including real-time review of DISE and PSG. For device titration PSGs, all participants are instructed to refrain from medications that may interfere with measurements in the sleep lab, including benzodiazepines, zopiclone, zolpidem and alcohol. Therapy optimisation is expected to take several months.

Participants are evaluated at 4, 6, 9 and 12 months postsurgery with optional visits at 3 and 5 months postsurgery (online supplemental table S1). If the therapy is not optimised by 6 months postsurgery, follow-up visits at 8 and 10 months are substituted for the 9 month visit. The coprimary endpoints and secondary endpoints are assessed at 12 months after surgery. Participants who choose to withdraw from the study early or who do not wish to participate

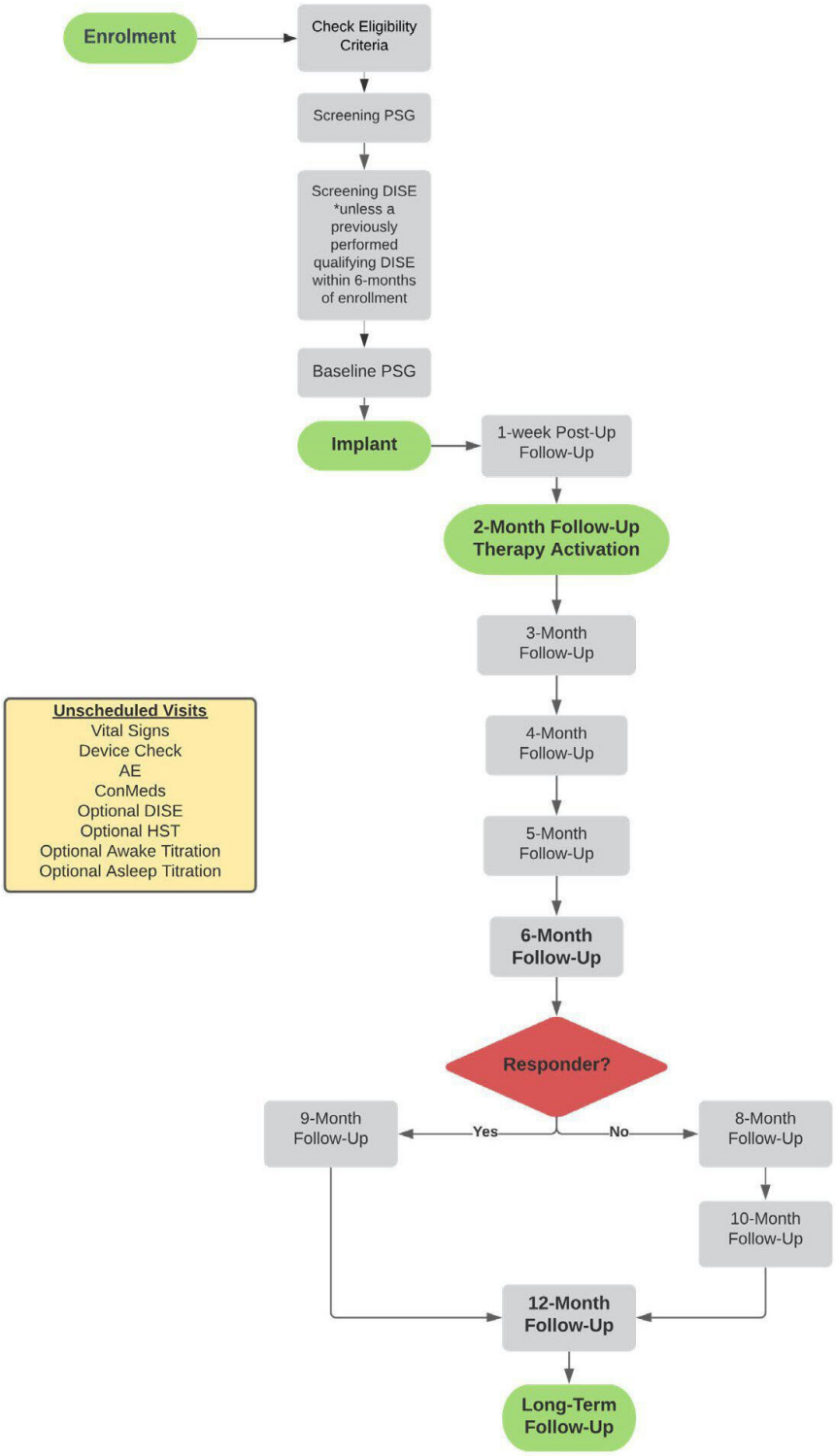

Figure 1 Flow chart of participant interventions throughout the study. AE, adverse event; DISE, drug-induced sleep endoscopy; HST, home sleep test; PSG, polysomnography.

in the follow-up study can either keep the IS in place and return all study-related equipment, rendering it inactive or undergo explanation surgery to remove the implant.

Endpoints assessed

Primary endpoints

Two coprimary effectiveness endpoints are used to evaluate the HNS_{BL} system 12 months following surgery: the AHI, with hypopnoeas associated with 4% oxyhaemoglobin desaturation (AHI4),[15 16] and the ODI4, using drops in oxygen concentration by at least 4% from baseline.[17 18] Scoring of these metrics are based on a full-night PSG scored by an independent core lab for all the study visits with a PSG. The first coprimary effectiveness endpoint as measured with fixed therapeutic settings

on full-night PSG is the percentage of responders at 12 months based on AHI4 (defined as participants with a 50% or greater reduction in AHI4 from baseline and AHI4 of less than 20 events per hour at 12 months postsurgery).[19] The second coprimary effectiveness endpoint is the percentage of responders at 12 months based on ODI4, defined as participants who have a 25% or greater reduction in ODI4 from baseline to 12 months postsurgery.

Secondary effectiveness endpoints

The secondary effectiveness endpoints include the mean change from baseline to the 12-month visit or 12-month PSG in:

- The Functional Outcomes of Sleep Questionnaire (FOSQ-10) to assess the impact of daytime sleepiness on activities of daily living.[20]
- The Symptoms of Nocturnal Obstruction and Related Events-25 instrument (SNORE-25) to assess the impact of treatment on OSA-specific quality of life.[21]
- The Epworth Sleepiness Scale (ESS) to assess daytime sleepiness.[22]
- The ODI4 to measure levels of intermittent hypoxia.
- The percentage of sleep time spent with less than 90% oxyhaemoglobin saturation to assess the change in hypoxaemic burden.
- The AHI4 to assess OSA severity.

Safety

The safety and tolerability of HNS_{BL} are assessed by recording the incidence of device-related SAEs during the study for a period of 12 months following surgery. Individual safety events are adjudicated by an independent clinical events committee (CEC), and an independent data safety and monitoring board (DSMB) reviews accumulating safety data from the study.

Statistical methods

All statistical analyses in this study are performed by using SAS software, V.9.4 or higher (SAS Institute). Continuous variables are summarised by a mean, SD, minimum, median and maximum, and categorical variables by absolute count and percentage. All statistical tests are one sided at 2.5% significance level. CIs are provided where relevant and appropriate, and the reported confidence level is 95% (two sided) unless otherwise specified. Worst-case imputation method is used primarily to impute missing data for the coprimary effectiveness endpoints. Missing values are considered non-responses. No interim analyses are planned for this study.

The coprimary effectiveness endpoint analyses test response to HNS_{BL} in the set of participants who successfully completed the implant procedure, had their device activated and completed at least one PSG. The study is considered successful if the null hypotheses are rejected for both coprimary effectiveness endpoints. Thus, each coprimary endpoint is tested at the 2.5% level of significance (one sided) without causing inflation of the type I error rate. The percentage of responders at 12 months is calculated with a two-sided 95% (equivalent to one-sided 97.5%) exact (Clopper-Pearson) CI, and the null hypotheses is rejected if the p value of the exact binomial test for one proportion comparing the percentages of responders to the prespecified performance goal of a 50% is <0.025. Supportive analyses of the coprimary effectiveness endpoints are conducted to assess the robustness of the results. They consist of reproducing the analyses (1) on the participants who do not have protocol deviations impacting the evaluation of these endpoints, (2) on the completers (ie, participants who completed the 12-month visit) and (3) using the last observation carried forward imputation method for missing data.

If the null hypotheses are rejected for the coprimary effectiveness endpoints, the secondary effectiveness endpoints are analysed to assess the effect size of HNS_{BL} in the set of participants who successfully completed the implant procedure and also in the set of participants who completed the full protocol without any major deviations. They are tested according to a hierarchical strategy based on a closed testing procedure to preserve an overall type I error rate of 2.5% (one sided). The mean change from baseline to the 12-month visit for each secondary effectiveness endpoint are evaluated in the following order:

1. Impact of daytime sleepiness on activities of daily living measured by FOSQ-10.
2. OSA-specific quality of life measured by SNORE-25.
3. Daytime sleepiness measured by ESS.
4. Intermittent hypoxia measured by ODI4.
5. Hypoxaemic burden measured by the percentage of sleep time with oxyhaemoglobin saturation<90%.
6. OSA severity was measured by AHI4.

Any changes in these endpoints are summarised with descriptive statistics and presented with two-sided 95% (equivalent to one-sided 97.5%) CI. A one-sided, one-sample, paired t-test is used to assess whether mean changes are significantly different from 0 (null hypothesis) with significance at 0.025.

Other effectiveness data collected during the course of the study are summarised descriptively by visit. For statistical tests of these endpoints, the significance of p values lower than 0.025 (one sided) is considered for exploratory purpose only.

The DREAM study will help establish the safety and effectiveness of HNS_{BL} in adults with moderate to severe OSA, addressing an unmet need for less morbid and more effective treatment options for OSA. The coprimary endpoint results and secondary endpoint results will be reported for the full analysis population (all participants who successfully completed the implant procedure, had their device activated and completed at least one PSG) and reported for the per-protocol (participants who completed the protocol without significant deviations) population if applicable. Participant follow-up will continue for 5 years to evaluate the long-term safety and effectiveness of reducing the severity of OSA through HNS_{BL}.

Safety analysis

The primary variable that is assessed for the safety analysis is the cumulative incidence of participants with device-related SAEs during 12 months postsurgery. The 100 mm pain visual analogue scale (VAS) is summarised at relevant scheduled visits, and descriptive summaries of other safety parameters, including number and percentage of participants with at least one AE and the absolute number of AEs, will be reported.

Data collection, sharing and study oversight

All required data for this trial are collected via electronic case report forms and securely entered into an electronic data capture system provided by the independent statistician. To continue to assess the safety and effectiveness of HNS_{BL}, implanted participants will be asked to return for in-person visits biannually for up to 5 years postsurgery. Recruitment started in late 2020, 12-month study results are anticipated to be available in late 2024, and 5-year results will be available in 2028.

The DSMB is composed of at least four members (three voting physicians from the field of otolaryngology-head and neck surgery and/or sleep medicine as well as one non-voting independent biostatistician), who are not directly involved in the conduct of the trial. The CEC evaluates study progress and to make recommendations concerning the continuation, modification or termination of the study. The CEC ensures objective and centralised review and adjudication of clinical AEs occurring in this study and is composed of at least three members (three physicians from the field of otolaryngology-head and neck surgery and/or sleep medicine), who are independent from the conduct of the study. To ensure compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements, Nyxoah SA may conduct a quality assurance assessment and/or audit of the site records during or after the completion of the study.

LIMITATIONS

Limitations of this protocol include the contribution made to the protocol design and data analysis plan by Nyxoah SA, which could potentially introduce bias into the study. This potential for bias has been minimised with several measures such as including outside medical experts in the design of the study including the FDA; the use of independent physician investigators for patient selection, data collection and oversight of study conduct at their sites; and the involvement of the CEC and DSMB to monitor participant safety during the study. Finally, the use of independent core labs to assess participant eligibility through DISE and PSG scoring avoids selection bias and allows for independent interpretation of the study results, respectively.

ETHICS AND DISSEMINATION

This study has been prospectively registered with ClinicalTrials.gov, number NCT03868618. The Food and Drug Administration, Advarra Institutional Review Board (IRB), University of Tennessee HSC IRB, University of Pennsylvania IRB, Weill Cornell Medicine IRB, Medical College of Wisconsin/Froedert Hospital, Human Research Protections Programme (HRPP) Vanderbilt University, St. Vincent's Hospital Melbourne Human Research Ethics Committee (HREC), Ethisch Comite Universitair Ziekenhuis Antwerpen and Technische Universitat Munchen reviewed and approved this protocol. The protocol received ethical approval from Advarra Institutional Review Board (IRB) on 6 July 2020, and enrolment began on 14 October 2020. The study is being conducted in accordance with all applicable regulatory requirements, including GCP and all applicable privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki (October 2013).

The primary endpoints and other results of this study will be disseminated via journal publications, ClinicalTrials.gov registry and the sponsor's website.

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Contributors BTW was the co-ordinating PI, review and oversight of study design and execution. MVS, MBG, TCH, MH and CH contributed to optimising the surgical technique and the eligibility criteria for the protocol. AS and JS refined the eligibility criteria, the schedule of events and the statistical analysis plan, and JS also refined device programming. FM and GF were independent statisticians who drafted the sample size calculation and statistical analysis plan. DTK contributed to the optimisation of the surgical technique and the eligibility criteria and to the refinement of the primary endpoint analysis. All authors critically revised and approved the manuscript. DTK is the guarantor of the contents.

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Competing interests BTW received research support from Nyxoah for work on the DREAM study and medical writing and consulting fees from Nyxoah, Medtronic and Cryosa, he holds company stock for the latter. MVS is an unpaid member of the International Surgical Sleep Society Board and has received direct payments for consulting and advising from Medtronic, payments for consulting and speaking from Nyxoah and Inspire Medical, and their institution has received funding from Nyxoah. MBG has received payments for consulting from Nyxoah and the Alfred Mann Foundation, and his institution has received support from Nyxoah and Inspire Medical. TCH received research support from Nyxoah for work on the DREAM study, and he has been a Data Safety Monitoring Board participant for the Osprey study by LivaNova. MH holds an unpaid position as President Florida Society of Facial and Reconstructive Surgery and her institution has received funding from Nyxoah. AS and JS are employees of Nyxoah and hold stock in the company. FM and GF

are employed by Inferential, which receives funding from Nyxoah for statistical and data services. CH has received grants/contracts and consulting fees from Nyxoah and Löwenstein Medical Products as well as consulting fees and speaker fees from Inspire Medical Products and XM Consult. DTK has received grant/contract funding, royalties/licences and consulting fees from Nyxoah, grant/contract funding and consulting fees from Invicta Medical, and grant/contract funding from the National Heart, Lung and Blood Institute, the American Academy of Sleep Medicine and Inspire Medical Systems.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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