Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator: Daniel Vena

Project Title: Combination tonsillectomy and hypoglossal nerve stimulation for OSA patients with lateral pharyngeal collapse.

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Version Name/Number: 07152026

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Obstructive Sleep Apnea (OSA) is a common and debilitating disorder due to collapse of one or more pharyngeal structures during sleep (velum, oropharyngeal lateral walls, tongue base, and/or epiglottis) [1, 2]. Standard treatment is continuous positive airway pressure (CPAP) but suffers from low adherence [3-6]. Hypoglossal nerve stimulation (HGNS) has emerged as a popular alternative therapy to CPAP. However, efficacy of HGNS therapy is highly dependent on the site of pharyngeal collapse [7-10]. Specifically, HGNS protrudes the tongue anteriorly and thus optimally treats patients with anteroposteriorly-directed pharyngeal collapse (e.g., tongue base obstruction). Whereas patients with a lateral component to their pharyngeal collapse, i.e. oropharyngeal lateral walls (OPLW) collapse, can respond inadequately to the treatment. Treatment options exist that can reduce the severity of the lateral component of collapse, such as tonsillectomy, expansion pharyngoplasty, lateral pharyngoplasty, maxillary expansion and maxillomandibular advancement. Each of these is options carry significant perioperative morbidity and/or do not address other regions of collapse. For example, tonsillectomy alone seldom eliminates sleep apnea, outside of the rare patient with tonsillar hypertrophy that experienced isolated tonsillar collapse. However, in combination with HGNS, tonsillectomy may be effective at eliminating the post-treatment residual OSA in patients with lateral walls collapse and is far less invasive than other options. The additional therapeutic effect of combining tonsillectomy with HGNS has never been investigated.

Table 1. Patient characteristics (median [IQR]).

	HGNS + LCi	HGNS alone (Control)
N	33	40
Age (years)	52 [42, 57]	57 [51, 67]
Men, n (%)	10 (83%)	12 (93%)
BMI (kg/m^2)	30 [28, 32]	30 [28, 32]
AHI (/h)	24 [15, 33]	32 [25, 37]
2+ tonsils	21	24

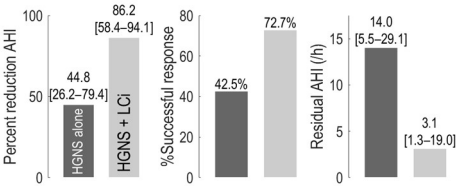


Fig 1. Treatment response in patients that underwent concomitant hypoglossal nerve stimulation and intervention to attenuate lateral pharyngeal collapse (HGNS+LCi) versus HGNS alone in terms of: percent reduction in apnea-hypopnea index (AHI, panel A), percentage of patients that achieved a successful treatment response (50% AHI reduction to <15/h) (panel B), and residual AHI with treatment (panel C). Unadjusted results are shown. Adjusted group differences are described in text.

In preliminary analysis, we present a prospective case-control study design that, in patients with complete OPLW collapse, combining HGNS with an intervention to alleviate lateral collapse (LCi) (i.e. tonsillectomy) substantially increased HGNS success, compared to HGNS alone (control)[11]. We studied a total of 73 patients with complete OPLW collapse who also had small tonsils and were implanted with HGNS. Among this group, 33 patients received concurrent intervention to alleviate lateral collapse (HGNS+LCi). Demographics and OSA severity were similar between groups (Table 1). Crude differences in the effect of HGNS were remarkable (Fig 1). In multivariable analysis, compared to HGNS alone, HGNS combined with LCi **increased the percent reduction AHI by 27.0 [12.6,38.7]%** (p=0.001, Fig 1A) adjusting for age, sex, BMI, and baseline AHI. Adjusted logistic regression showed that adding LCi provided a **6-fold increase in odds** of a successful therapeutic response (50% AHI reduction to <15 /h; odds ratio[95%CI]: 5.5 [1.6,19.0], p=0.009, Fig 1B). **Residual AHI was also reduced 4-fold** (Fig 1C). In other words, removing the tonsils in this sample of OPLW collapse patients resulted in a potent and near-complete treatment response to HGNS that resembles that of non-OPLW collapse.

Accordingly, the objective of the current study is to formally investigate the benefit of combining tonsillectomy with HGNS treatment in patients with complete OPLW collapse. We hypothesize that in patients with complete OPLW collapse that are candidates for HGNS, combining tonsillectomy with HGNS will significantly improve treatment response over HGNS alone. The proposed research is likely to be highly significant, as it will be the first to investigate a simple adjunctive treatment option to treat residual OSA in a patient subgroup that are often implanted, but inadequately treated with HGNS.

2. Specific Aims and Objectives

Aim 1. Determine the effect of HGNS plus tonsillectomy versus HGNS alone on OSA severity in patients with complete oropharyngeal lateral wall collapse.
In a randomized controlled trial 72 patients with oropharyngeal lateral wall (OPLW) collapse who are candidates for both HGNS and tonsillectomy will be randomly assigned to either: 1) concurrent HGNS plus tonsillectomy, or 2) HGNS alone (with optional delayed tonsillectomy). We will assess whether HGNS plus tonsillectomy increases treatment efficacy compared to HGNS alone.

Aim 2. Determine whether tonsillectomy enhances HGNS-induced improvement in pharyngeal collapsibility in patients with complete oropharyngeal lateral wall collapse.
In a subset of 30 participants (15 per treatment group), we will assess whether HGNS combined with tonsillectomy produces greater HGNS-induced improvements in pharyngeal collapsibility compared with HGNS alone.

Aim 3. Determine whether tonsillectomy acts as a modifier on the effect of HGNS.
In the same cohort of 72 participants described in Aim 1, we will evaluate whether the combined effects of HGNS and tonsillectomy are additive or synergistic. Specifically, we will examine whether HGNS-related outcomes, including treatment efficacy and pharyngeal collapsibility, are greater when HGNS is delivered in the presence of tonsillectomy compared with HGNS alone.

3. General Description of Study Design

This study is a prospective, randomized, controlled interventional trial designed to evaluate the effect of combining tonsillectomy with hypoglossal nerve stimulation (HGNS) in adults with obstructive sleep apnea (OSA) and complete oropharyngeal lateral wall (OPLW) collapse.

Participants will be screened as part of their standard clinical evaluation for HGNS therapy, including drug-induced sleep endoscopy (DISE) to characterize the pattern of pharyngeal collapse. Individuals meeting eligibility criteria for the study, including complete OPLW collapse and candidacy for both HGNS implantation and tonsillectomy, will be enrolled and complete a baseline polysomnography (PSG1; in-lab or at-home) to confirm OSA severity.

Following baseline assessment, participants will be randomized in a 1:1 ratio to one of two treatment arms:

1. **Concurrent HGNS plus tonsillectomy (HGNS+LCi)**, or
2. **HGNS alone**, with the option for delayed tonsillectomy later in the study if clinically indicated.

All participants will undergo HGNS implantation, followed by standard post-operative activation and titration per clinical protocol. HGNS activation will occur approximately four weeks after implantation, with subsequent optimization of stimulation settings over the following months.

Treatment efficacy will be assessed after one month of optimized HGNS therapy using PSG and patient-reported outcomes, constituting the primary study endpoint. Participants in the HGNS+LCi group will additionally undergo a study-specific HGNS-off assessment to isolate the physiological effect of tonsillectomy alone. Participants randomized to HGNS alone who demonstrate residual OSA will be offered delayed tonsillectomy, followed by additional assessments with HGNS on and off to allow evaluation of combined versus individual treatment effects.

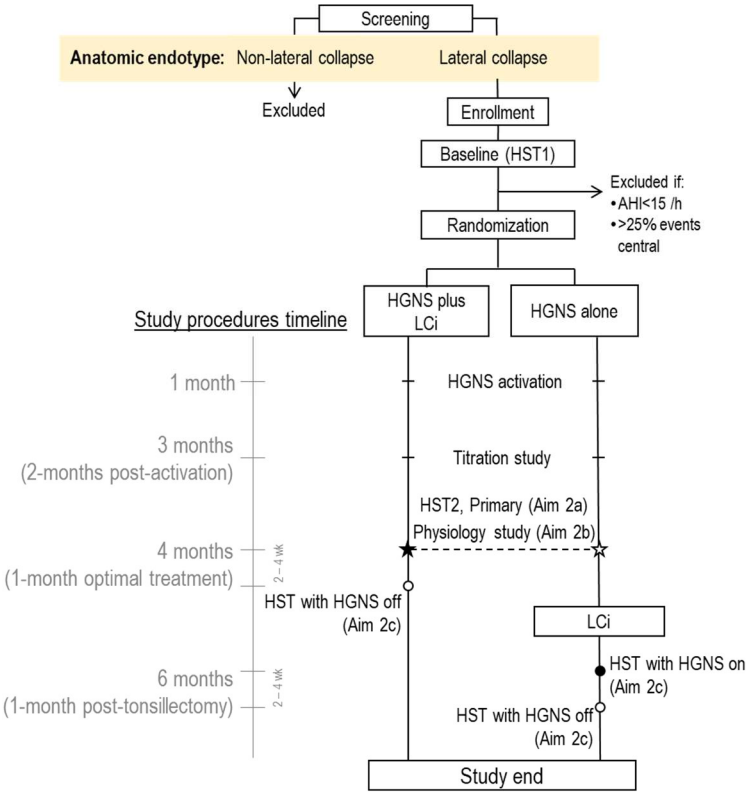


Fig 2. Study schema and timeline of study procedures. The stars (☆) indicate study procedures used to assess the primary study endpoint (short-term efficacy). Filled shapes represent study procedures assessing the effect of HGNS plus surgical intervention for laterally-directed collapse (HGNS+LCi). Open shapes represent study procedures assessing the effects of individuals treatments (HGNS alone or LCi alone).

A subset of participants from each treatment arm will undergo an in-laboratory physiological sleep study to assess pharyngeal collapsibility using gold-standard methods. These measurements will be used to evaluate whether tonsillectomy enhances HGNS-induced improvements in airway collapsibility and to explore whether the combined effects of HGNS and tonsillectomy are additive or synergistic.

The overall study schema, sequence of interventions, and timing of assessments are summarized in **Figure 1**.

4. Subject Selection

The study population will consist of adult patients with obstructive sleep apnea (OSA) who are undergoing clinical evaluation for hypoglossal nerve stimulation (HGNS) therapy and are found to have complete oropharyngeal lateral wall (OPLW) collapse on drug-induced sleep endoscopy (DISE).

Inclusion Criteria
Participants must meet **all** of the following criteria to be eligible for enrollment:

1. Age ≥ 18 years
2. Diagnosis of obstructive sleep apnea with apnea–hypopnea index (AHI) ≥ 15 events/hour
3. Complete oropharyngeal lateral wall (OPLW) collapse identified on DISE
4. Candidate for HGNS implantation based on standard clinical criteria
5. Presence of small (1-2+) tonsils and eligibility for tonsillectomy
6. Untreated OSA at the time of enrollment
7. Willing and able to provide written informed consent

Exclusion Criteria
Participants meeting **any** of the following criteria will be excluded:

1. Absence of tonsils
2. Presence of large tonsils (3-4+; not eligible for HGNS)
3. Predominant central or mixed sleep apnea (>25% central or mixed events)
4. Any unstable or serious medical condition that, in the opinion of the investigator, would increase risk or interfere with study participation
5. Ineligibility for HGNS implantation based on standard clinical or surgical criteria
6. Inability to comply with study procedures or follow-up assessments

Rationale for Subject Selection
This study focuses specifically on patients with complete OPLW collapse, as this anatomical pattern has been associated with reduced efficacy of HGNS and represents a clinically relevant subgroup that is commonly implanted but often inadequately treated. Tonsillectomy targets the lateral pharyngeal walls and is therefore mechanistically aligned with the hypothesized cause of HGNS non-response in this population. Patients with complete concentric collapse (CCC) are excluded because HGNS is not standard therapy for this group and because the current study is designed to isolate the effect of tonsillectomy in OPLW collapse specifically.

5. Subject Enrollment

Identification and Pre-screening
Potential participants will be identified from patients undergoing routine clinical evaluation for hypoglossal nerve stimulation (HGNS) in the practice of Dr. Phillip Huyett. As part of standard clinical care, patients undergo diagnostic sleep testing and drug-induced sleep endoscopy (DISE) to determine HGNS candidacy and characterize the pattern of pharyngeal collapse. Patients with complete oropharyngeal lateral wall (OPLW) collapse who are candidates for both HGNS and tonsillectomy will be offered combined HGNS plus tonsillectomy as a standard clinical treatment option. **Only patients who, after discussion of available treatment options, indicate that they wish to proceed with HGNS combined with tonsillectomy will be considered for participation in the research study.**

During the same clinical visit, the treating surgeon will briefly introduce the research study and ask whether the patient is willing to be contacted by study staff. Only patients who provide verbal permission will be contacted. Limited pre-screening by telephone or secure email may be conducted by study staff to confirm basic eligibility. No research-specific screening procedures will be performed prior to informed consent, and no separate screening consent will be obtained.

Pregnancy testing is not a study procedure. Standard institutional pregnancy testing policies for surgical patients will apply as part of routine clinical care, independent of research participation.

Consent Process
Written informed consent will be obtained prior to the performance of any study-specific procedures. Consent will be obtained in a private setting, either in person or remotely using Mass General Brigham–approved consenting procedures, as applicable.

Informed consent will be obtained by the Principal Investigator (Daniel Vena, PhD), with licensed physician backup, or by a licensed physician co-investigator (e.g., Phillip Huyett, MD; Andrew Wellman, MD), prior to any study procedures. Appropriately trained study staff may assist with the consent process (e.g., providing the consent form and answering general questions), but a licensed physician investigator will conduct the consent discussion, confirm participant understanding, and obtain written informed consent.

Participants will receive a detailed explanation of the study purpose, procedures, randomization, risks, potential benefits, alternatives, and expected time commitment using a prepared script included with this application. Participants will be provided a copy of the informed consent document and allowed a minimum of 24 hours to review the information and decide on participation. Study investigators will be available to answer any questions during this period.

This study enrolls adults only (≥18 years). Participants must have the capacity to provide informed consent; surrogate consent will not be used. Study materials and consent discussions will be conducted in English or, when needed, using IRB-approved translated consent documents and qualified interpretation services to ensure meaningful participation by individuals who do not speak English.

To minimize undue influence when recruiting patients of the treating surgeon, all participants will be explicitly informed that participation is voluntary, that they may decline or withdraw at any time, and that their decision will not affect their current or future medical care. Participants will be offered the opportunity to discuss the study in more detail with a study team member other than the treating surgeon. Participants will be provided a copy of the consent form, encouraged to take additional time to consider participation, and given the opportunity to discuss the study with family members or other health care providers before making a decision.

Enrollment and Randomization

After informed consent and confirmation of eligibility, participants will be enrolled and will schedule baseline study assessments, including a baseline sleep study (i.e., in-lab or home sleep test).

Participants will then be randomized in a 1:1 ratio to either:

1. HGNS implantation with concurrent tonsillectomy, or
2. HGNS implantation alone, with the option for delayed tonsillectomy later in the study.

Randomization will occur prior to surgery using a computer-generated randomization schedule with permuted blocks to maintain approximate balance between groups over time. The randomization schedule will be maintained by a study team member who is not otherwise involved in participant recruitment, consent, outcome assessment, or data analysis. After informed consent is obtained and eligibility is confirmed, treatment assignment will be communicated only to the treating surgeon and other personnel who require the information for operative planning. Because treatment assignment determines the surgical procedure performed, the treating surgeon cannot be blinded. However, study personnel involved in outcome assessment and primary data analysis will remain blinded to treatment assignment whenever feasible, with analyses performed using coded treatment labels. Participants may withdraw from the study at any time without penalty or impact on their clinical care.

Repeat Assessments and Communication

If data are deemed insufficient due to technical issues or incomplete recordings, participants may be asked to repeat study components.

All electronic communications containing confidential information will comply with Mass General Brigham security policies, including encrypted email when required. Video visits will use the MGB-approved videoconference platform.

6. STUDY PROCEDURES

Overview of Study Visits and Procedures

This study includes a combination of standard clinical procedures and study-specific assessments. Standard clinical procedures include hypoglossal nerve stimulation (HGNS) implantation, tonsillectomy when applicable, device activation, and titration. Study-specific procedures consist of sleep studies (in-lab PSG or home sleep testing), questionnaires, and, in a subset of participants, an in-laboratory physiological sleep study. A summary schedule of study visits and assessments is provided at the end of this section.

Study Visit	Procedures
Baseline	Consent, eligibility confirmation, baseline sleep study, questionnaires
Surgery	HGNS implantation ± tonsillectomy
Activation/Titration	HGNS activation and optimization
Primary Follow-up	Sleep study, questionnaires
Mechanistic Testing	HGNS on/off sleep studies, delayed tonsillectomy pathway as applicable
Sub-study (optional)	In-lab physiological sleep study

Baseline Visit
After informed consent and confirmation of eligibility, participants will complete baseline study assessments. These include:

- Collection of demographic and clinical data
- Baseline sleep study (PSG1) to assess OSA severity if a qualifying diagnostic study is not available
- Baseline questionnaires assessing sleepiness, sleep quality, and sleep-related quality of life

Data collected at baseline will include apnea–hypopnea index (AHI), oxygen desaturation metrics, and questionnaire scores.

Randomization
After completion of baseline assessments, participants will be randomized in a 1:1 ratio to one of two treatment arms:

1. HGNS implantation with concurrent tonsillectomy (HGNS+T)
2. HGNS implantation alone (HGNS-only), with the option for delayed tonsillectomy later in the study if clinically indicated

Randomization will occur prior to surgery using a study-specific randomization scheme.

Surgical Procedures
All participants will undergo HGNS implantation as part of standard clinical care using an FDA-approved device and standard surgical techniques. Participants randomized to the HGNS+T arm will undergo tonsillectomy during the same operative session. Participants randomized to the HGNS-only arm will undergo HGNS implantation without tonsillectomy.

No investigational drugs or investigational devices will be used as part of this study. HGNS implantation and tonsillectomy will be performed entirely within their FDA-approved and standard-of-care indications. No off-label dosing, programming, or surgical techniques will be employed. As no investigational devices are being studied, an investigational device exemption (IDE) is not required.

Postoperative Care, Activation, and Titration
Postoperative care will follow standard clinical protocols. HGNS will be activated approximately four weeks after implantation. Device programming and titration will be performed according to routine clinical practice to optimize therapeutic efficacy. No study-mandated deviations from standard HGNS programming will occur.

Postoperative pain management will be provided according to standard clinical practice. Analgesic medications, which may include non-opioid and opioid pain medications, may be prescribed at the discretion of the treating surgeon based on clinical need. No study-specific pain management protocols will be mandated. Information on postoperative analgesic use will be collected for descriptive and safety monitoring purposes only.

Primary Follow-up Assessment
After approximately one month of optimized HGNS therapy, participants will complete the primary follow-up assessment, which includes:

- Follow-up sleep study (PSG2) to assess treatment efficacy
- Repeat questionnaires assessing sleepiness, sleep quality, and treatment satisfaction

The primary study endpoint will be assessed at this timepoint.

Additional Sleep Testing for Mechanistic Comparisons
To support mechanistic analyses:

- Participants in the HGNS+T arm will complete an additional sleep study with HGNS temporarily turned off to isolate the effect of tonsillectomy alone.
- Participants in the HGNS-only arm who demonstrate residual OSA may elect to undergo delayed tonsillectomy as part of standard clinical care. Following recovery, these participants will complete additional sleep study with HGNS on and with HGNS off.

These additional assessments are intended to evaluate the combined versus individual effects of HGNS and tonsillectomy.

Physiological Sub-study
A subset of approximately 30 participants (15 per treatment arm) will be invited to participate in an optional in-laboratory physiological sleep study. This study will assess pharyngeal collapsibility using established techniques, including controlled reductions in positive airway pressure during sleep. Data collected will include measures of upper airway collapsibility (e.g., critical closing pressure), ventilation, and airflow. Participation in this substudy is optional and not required for participation in the main trial.

Data Collection
Data collected in this study will include:

- Demographic and clinical characteristics
- Sleep study metrics (e.g., AHI, oxygen desaturation index, hypoxic burden)
- HGNS device settings and usage data
- Questionnaire-based patient-reported outcomes
- Postoperative pain medication use collected via medical record review and participant self-report.
- Physiological measurements of pharyngeal collapsibility in sub-study participants

Data will be collected using standardized clinical reports, electronic case report forms, and validated questionnaires.

Pregnancy Testing
Pregnancy testing is not a study-specific procedure. Pregnancy testing for participants of reproductive potential will be performed in accordance with standard institutional policies for surgical patients as part of routine clinical care, independent of research participation.

Return of Research Results and Incidental Findings
Participants will receive clinically relevant results from their sleep studies through their treating clinical team as part of standard care. Aggregate study results may be shared with participants upon study completion. No genetic results will be generated. Incidental findings of potential clinical significance will be communicated to participants through appropriate clinical channels.

Outcomes and Endpoints
The primary outcome is percent reduction in apnea–hypopnea index (AHI) following HGNS therapy.

Secondary outcomes include:

- Absolute change in AHI
- Treatment success (defined as ≥50% reduction in AHI and AHI <15 events/hour)
- Measures of pharyngeal collapsibility
- Patient-reported outcomes related to sleepiness and sleep quality

All outcomes are quantifiable and measurable.

Study Termination Criteria
Participants may be withdrawn from the study for any of the following reasons:

- Participant request
- Clinical decision to discontinue HGNS or surgical therapy
- Occurrence of unacceptable adverse events
- Investigator determination that continued participation is not in the participant's best interest

Participants who withdraw will continue to receive standard clinical care.

End of Study or Early Withdrawal
Participation in the study will not affect access to clinical care. Participants who complete or withdraw from the study will continue to receive routine clinical follow-up and management of their OSA. Data collected prior to withdrawal may be retained for analysis unless the participant requests otherwise, in accordance with IRB policy.

Remuneration
Participants will receive compensation for completion of specific study procedures. Participants who complete the baseline and primary follow-up study procedures, including sleep studies and questionnaires, will receive **$150**. Participants who complete additional sleep studies performed for mechanistic comparisons will receive **$75 per sleep study** (i.e., **$75** for the single additional sleep study in the HGNS plus tonsillectomy arm, and **$175** for two additional sleep study in participants randomized to HGNS alone who subsequently undergo tonsillectomy). Participants who take part in the optional in-laboratory physiological sub-study will receive an additional **$200**. This amounts to a total of up to **$450 for the HGNS plus tonsillectomy** arm and **$525 for participants randomized to HGNS alone who subsequently undergo tonsillectomy**.

If a sleep study must be repeated due to insufficient or technically inadequate data, no additional compensation will be provided for repeat testing.

Study funds will also cover reasonable parking and transportation costs associated with study visits, up to a total of $100.

7. Risks and Discomforts

Risks of Surgical Procedures

Hypoglossal Nerve Stimulation (HGNS) Implantation
HGNS implantation is an FDA-approved surgical procedure and is part of routine clinical care for eligible patients with obstructive sleep apnea. Potential risks include, but are not limited to, pain, bleeding, infection, swelling, scarring, nerve injury, discomfort at the implant site, tongue weakness, tongue soreness, speech or swallowing changes, and the need for device revision or removal. Risks related to anesthesia include nausea, vomiting, sore throat, cardiovascular or respiratory complications, and, rarely, serious adverse events.

Tonsillectomy
Tonsillectomy is a commonly performed surgical procedure. Risks include postoperative pain, bleeding (which may require medical or surgical intervention), infection, dehydration, difficulty swallowing, changes in voice, and risks related to anesthesia. Delayed postoperative bleeding may occur in a small proportion of patients. Postoperative pain following tonsillectomy may require prescription pain medications, including opioids, which carry risks such as nausea, constipation, sedation, dizziness, and, rarely, dependence or misuse. Pain management will follow standard clinical practice.

Both surgical procedures will be performed by experienced surgeons using standard techniques, and perioperative care will follow institutional best practices to minimize risk.

Risks of Non-Surgical Study Procedures

Sleep study
Sleep studies, either in the form of in-lab PSG or home sleep test, are non-invasive and considered low risk. Potential discomforts include minor skin irritation from sensors, discomfort wearing monitoring equipment during sleep, and possible sleep disruption.

In-Laboratory Physiological Sleep Study (Substudy)
Participants in the optional physiological substudy may experience discomfort related to wearing sensors, sleeping in a laboratory environment, or transient sleep disruption. The protocol may involve brief reductions in positive airway pressure to assess airway collapsibility, which could cause short-term breathing discomfort or sleep fragmentation. These procedures are commonly used in sleep research and will be conducted under close monitoring by trained personnel.

Drug-Induced Sleep Endoscopy (DISE)
DISE involves administration of sedative medications as part of routine clinical evaluation or, in some cases, a research-specific procedure. Risks include those associated with sedation, such as breathing suppression, changes in blood pressure or heart rate, nausea, vomiting, or allergic reactions. DISE will be performed in a monitored setting by experienced clinicians.

Device-Related Risks
The HGNS system is an FDA-approved medical device used according to standard clinical indications. Potential device-related risks include device malfunction, lead displacement, discomfort related to stimulation, infection involving the device, or need for device reprogramming or revision. No investigational devices are being tested in this study.

Pregnancy-Related Risks
This study does not involve administration of investigational drugs or radiation exposure. Surgical procedures and anesthesia carry potential risks to a pregnant individual and fetus. Pregnancy testing will be performed in accordance with standard institutional policies for surgical patients of reproductive

potential as part of routine clinical care. Pregnant individuals will not undergo elective surgical procedures inconsistent with clinical standards.

Questionnaires
Participants will complete questionnaires that contain personal information (e.g. about sleep, fatigue and intimacy). Patients will be advised that they do not have to answer any questions that make them uncomfortable.

Privacy and Confidentiality Risks
There is a potential risk of loss of confidentiality of personal health information. Measures to minimize this risk include secure storage of data, use of coded identifiers, restricted access to study data, encrypted electronic communications when required, and adherence to Mass General Brigham privacy and security policies. These protections are described in greater detail in the Privacy and Confidentiality section of this protocol.

Risk Minimization
Risks to participants are minimized by the following measures:

- Study procedures are consistent with sound research design and are necessary to address the study objectives.
- Whenever possible, procedures used in this study are identical to those already being performed as part of routine clinical care.
- No investigational drugs or devices are used.
- Optional research procedures (e.g., physiological substudy) are not required for participation in the main trial.
- Participants are closely monitored during and after procedures, and adverse events are promptly evaluated and managed.
- Participants may withdraw from the study at any time without affecting their clinical care.

Overall, the incremental risks associated with research participation beyond standard clinical care are minimal and primarily related to additional sleep testing and optional physiological measurements.

8. Benefits

Participants may **not receive any direct benefit** from participation in this research study. All surgical and device-based treatments provided in this study, including hypoglossal nerve stimulation (HGNS) implantation and tonsillectomy when applicable, are offered as part of standard clinical care independent of research participation. Decisions regarding clinical treatment are made prior to and separately from study enrollment.

Participation in the study may result in **no additional therapeutic benefit beyond standard clinical care**. However, participants may experience indirect benefits, such as additional sleep testing, closer monitoring of treatment response, and more detailed assessment of obstructive sleep apnea severity, which may inform ongoing clinical management. These indirect benefits are not guaranteed.

Potential benefits do not differ substantially between study groups, as all participants receive clinically indicated care regardless of study assignment. Participants randomized to combined HGNS and tonsillectomy or HGNS alone may or may not experience improvement in obstructive sleep apnea symptoms, consistent with usual clinical outcomes.

The primary benefit of this study is to society. The information gained may improve understanding of the role of oropharyngeal lateral wall collapse in response to HGNS therapy and clarify whether combining tonsillectomy with HGNS improves treatment outcomes. Results from this study may help guide future patient selection, optimize treatment strategies, and improve care for patients with obstructive sleep apnea.

9. Statistical Analysis

All statistical analyses will be conducted to evaluate the clinical and physiological effects of combining tonsillectomy with hypoglossal nerve stimulation (HGNS) in patients with complete oropharyngeal lateral wall collapse. Analyses will be aligned with the prespecified study aims and will follow an intention-to-treat framework unless otherwise specified. Statistical significance will be assessed using two-sided tests with a significance level of $\alpha = 0.05$.

Aim 1: Effect of HGNS Plus Tonsillectomy Versus HGNS Alone on OSA Severity
The **primary endpoint** is HGNS treatment response, defined as **percent reduction in apnea–hypopnea index (AHI)** from baseline sleep study to the primary follow-up sleep study after approximately one month of optimized HGNS therapy.

The primary comparison will assess differences in percent AHI reduction between randomized groups (HGNS plus tonsillectomy versus HGNS alone) using linear regression models. Baseline AHI and other relevant covariates (e.g., age, sex, body mass index) may be included to improve precision. If distributional assumptions are violated, transformation or robust regression methods may be used, with results reported on the original scale.

Secondary endpoints include absolute change in AHI, treatment success (defined as ≥50% reduction in AHI to <15 events/hour), oxygenation metrics (e.g., oxygen desaturation index and hypoxic burden), and patient-reported outcomes. Continuous secondary outcomes will be analyzed using linear regression, and binary outcomes (e.g., treatment success) will be analyzed using logistic regression.

All participants will be analyzed according to their randomized treatment assignment in the primary intention-to-treat analysis.

Aim 2: Effect of Tonsillectomy on HGNS-Induced Improvement in Pharyngeal Collapsibility
In the physiological substudy, the primary endpoint is **HGNS-induced change in pharyngeal collapsibility**, quantified as the difference in critical closing pressure (ΔPcrit) measured with HGNS on versus off.

In the subset of 30 participants (15 per group), ΔPcrit will be compared between treatment arms using linear regression or equivalent two-sample comparisons. If repeated measurements are obtained within participants, mixed-effects models with participant-level random intercepts will be used. Covariate adjustment may be included as appropriate.

Aim 3: Effect Modification and Synergy Between HGNS and Tonsillectomy
To determine whether tonsillectomy modifies the effect of HGNS (i.e., whether effects are additive or synergistic), mixed-effects models will be used incorporating within-subject comparisons from

mechanistic sleep studies. Models will include fixed effects for HGNS condition (on/off), tonsillectomy status (present/absent), and the **HGNS × tonsillectomy interaction**, with participant-level random intercepts to account for repeated observations.

A statistically significant interaction term will be interpreted as evidence that tonsillectomy modifies the physiological or clinical effect of HGNS beyond additivity.

Power and Sample Size

Aim 1 (Primary Clinical Trial):
A total of **72 participants (36 per group)** provides **80% power** at a two-sided $\alpha = 0.05$ to detect an **18% greater reduction in AHI** (percent change from baseline) in the HGNS plus tonsillectomy group compared with HGNS alone. Power exceeds **90%** to detect the **27% improvement** observed in preliminary data. These calculations assume standard deviations of **26.3%** in the HGNS plus tonsillectomy group and **27.2%** in the HGNS-alone group.

Aim 2 (Physiological Substudy):
A total of **30 participants (15 per group)** provides **82% power** to detect a **2.2 cmH_2O** greater HGNS-induced improvement in pharyngeal collapsibility (ΔPcrit) in the HGNS plus tonsillectomy group, assuming standard deviations of **2.3 cmH_2O** for HGNS alone and **2.0 cmH_2O** for HGNS plus tonsillectomy.

Aim 3 (Synergy Analysis):
It is anticipated that approximately **18 participants** randomized to HGNS alone will subsequently undergo tonsillectomy and complete HGNS on/off sleep studies, yielding approximately **144 observations across 72 participants**. Simulation studies (10,000 replications) demonstrate **99% power** to detect a **15% interaction effect** attributable to tonsillectomy, representing the threshold for synergistic modification of the HGNS effect.

Missing or Inadequate Data

Sleep studies that are technically inadequate may be repeated as described in the study procedures. Primary analyses will use all available data under an intention-to-treat framework. Sensitivity analyses may be performed to assess the impact of missing data on study conclusions.

10. Monitoring and Quality Assurance

Overview of Safety Oversight
This study will be conducted under the oversight of the Mass General Brigham Institutional Review Board (IRB). Participant safety, data integrity, and protocol adherence will be monitored throughout the study. Given that the study involves surgical interventions and a randomized comparison of treatment strategies, an independent Data and Safety Monitoring Board (DSMB) will be established to provide additional oversight.

Adverse Event Monitoring and Reporting

All adverse events (AEs) will be monitored and recorded throughout the study period. Adverse events include any untoward medical occurrences temporally associated with study participation, whether or not they are considered related to study procedures.

Serious adverse events (SAEs) will be defined in accordance with standard regulatory criteria and include events that result in death, are life-threatening, require hospitalization or prolongation of hospitalization, result in significant disability, or require medical or surgical intervention to prevent such outcomes.

AEs and SAEs will be assessed for severity, expectedness, and relatedness to study procedures. All unanticipated problems involving risk to participants or others and all SAEs will be reported to the IRB in accordance with institutional reporting requirements and timelines. Device-related or procedure-related adverse events will also be reported to the study sponsor and regulatory authorities as required.

Postoperative and device-related adverse events will be monitored clinically by the treating surgeon. The Principal Investigator and clinical investigators will remain available to participants to address safety concerns and coordinate clinical care or referral as needed.

Planned Safety Monitoring and DSMB Oversight
An independent DSMB will be convened following study initiation and will oversee participant safety throughout the trial. The DSMB will be independent of the study team and will have the authority to review study progress, participant safety, and data quality, and to recommend study continuation, modification, or termination based on safety findings.

The DSMB will review accumulated safety data and study conduct at regular intervals, anticipated to occur at study initiation and approximately every six months thereafter. Additional ad hoc reviews may be conducted if safety concerns arise. A description of the DSMB composition, meeting frequency, and responsibilities is provided in **Appendix A (DSMB Appendix)**.

Outcomes Monitoring
Study outcomes, including treatment response and safety endpoints, will be monitored on an ongoing basis by the study team. Aggregate outcome data will be reviewed periodically to ensure that observed results do not raise safety concerns that would warrant protocol modification or early study termination.

Study Stopping Rules
The study may be paused or terminated early if any of the following occur:

- An unexpected frequency or severity of serious adverse events related to study procedures
- DSMB recommendation to suspend or terminate the study due to safety concerns
- Determination by the Principal Investigator or IRB that continued participation poses unacceptable risk

Internal Monitoring and Quality Assurance
The Principal Investigator will be responsible for internal monitoring of protocol adherence, data completeness, and data accuracy. Study staff will conduct regular reviews of source documents, case report forms, and electronic data entries to ensure consistency and completeness. Protocol deviations and data quality issues will be documented and addressed in a timely manner.

All study personnel will complete required training in human subjects protection, Good Clinical Practice, and institutional privacy and security policies prior to participating in study activities.

Independent Monitoring
No independent source-data monitoring is required beyond DSMB oversight, as this study does not involve investigational drugs or investigational devices and does not meet criteria for FDA-regulated significant-risk device monitoring.

Data Management
Study data will be collected using standardized data collection forms and stored using coded participant identifiers. Electronic data will be maintained on secure Mass General Brigham–approved systems with restricted access limited to authorized study personnel. Data will be backed up regularly in accordance with institutional policies. Procedures for maintaining confidentiality and data security are described in greater detail in the Privacy and Confidentiality section of this protocol.

11. Data and Research Material Sharing

A) Sending Data/Materials to Research Collaborators outside Mass General Brigham

De-identified or coded study data may be shared with research collaborators outside Mass General Brigham for the purposes of data analysis, interpretation, or scientific dissemination. Data shared will be limited to the minimum necessary to achieve the scientific objectives of the study and will not include direct identifiers. Any sharing of data will occur only after approval by the Principal Investigator and in accordance with Mass General Brigham policies, applicable data use agreements, and IRB approvals, as required. No biological specimens will be shared as part of this study.

B) Receiving Data/Materials from Research Collaborators outside Mass General Brigham

This study does not involve receiving data or research materials from external collaborators outside Mass General Brigham.

12. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting.
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected.
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol.
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies.
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research.
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens.
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research.
- ☐ Additional privacy and/or confidentiality protections

13. References

ENTER TEXT HERE

APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required* if this Appendix has been completed and approved by the IRB.

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☒ The DMC/DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☒ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:
The DSMB will consist of 3 independent members with expertise relevant to the study, which may include sleep medicine, otolaryngology/sleep surgery, biostatistics, and clinical trial oversight. Members will have no direct involvement in the conduct of the study.

☒ Describe planned frequency of meetings:
The DSMB will review safety data following study initiation and at regular intervals, anticipated to be approximately every six months, with additional ad hoc meetings convened as needed in response to safety concerns or at the request of the DSMB or Principal Investigator.

☒ DMC/DSMB reports with no findings (i.e., “continue without modifications”) will be submitted to the IRB at the time of Continuing Review.

☒ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.