TITLE PAGE

FULL/LONG TITLE OF THE EXPERIMENT
Assessment of the effect of hypoglossal nerve stimulation therapy on upper airway collapsibility during drug-induced sleep endoscopy.

SHORT TITLE OF THE EXPERIMENT/ ACRONYM
HNS-CoDSE

PROTOCOL VERSION NUMBER AND DATE
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the experiment in compliance with the approved protocol and will adhere to the general principles outlined in the requirements for the conduct of clinical experiment in the GCP guidelines, latest version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on humans, and other regulatory requirements as amended.
I confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the experiment will be given; and that any discrepancies from the experiment as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:	
Signature:	Date: ...../...../.....
Name and position:	
Principal Investigator:	
Signature:	Date: ...../...../.....
Name and position: **.....** **.....**	

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AHI	Apnea-Hypopnea Index
BIS	Bispectral Index
BMI	Body Mass Index
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
(e)CRF	(electronic) Case Report Form
DISE	Drug-Induced Sleep Endoscopy
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiography
EEG	Electroencephalogram
EMG	Electromyography
ESS	Epworth Sleepiness Scale
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HNS	Hypoglossal Nerve Stimulation
ICF	Informed Consent Form
ICH	International council on Harmonisation of technical requirements for registration of pharmaceuticals for human use
(e)ISF	(electronic) Investigator Site File
O2	Oxygen
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
P_{crit}	Pharyngeal critical closing pressure
PI	Principle Investigator
PM	Project Manager
PSG	Polysomnography
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SC	Study Co-ordinator
SpO2	Oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCI	Target Controlled Infusion
TMG	Trial Management Group
TSC	Trial Steering Committee
(e)TMF	(electronic) Trial Master File
VAS	Visual Analogue Scale
ΔPcrit	Change in pharyngeal critical closing pressure

VERSION HISTORY LOG

This table should detail the version history for this document. The key elements of the changes to the versions should be detailed here.

DOCUMENT HISTORY		
VERSION NUMBER	**DATE** (DDMMMYYYY)	**SECTIONS THAT HAVE BEEN ADAPTED (WITH SHORT DESCRIPTION AND NAME OF THE PERSON WHO MADE THE ADAPTATIONS)**
1.0	**04112025**	**/**

SUMMARY

Title of the experiment	Assessment of the effect of hypoglossal nerve stimulation therapy on upper airway collapsibility during drug-induced sleep endoscopy.	
Short title	HNS-CoDSE (Hypoglossal Nerve Stimulation effect on Collapsibility during Drug-induced Sleep Endoscopy)	
Internal reference (if applicable)/ CTMS number	EDGE-004441	
Clinicaltrials.gov	<xxxxxxxxxxx>	
Design of the experiment	Prospective interventional study	
Participants and setting	Patients with moderate to severe OSA (AHI>15/h) receiving HNS treatment at the ENT department at Antwerp University Hospital.	
Intervention(s)	Routine DISE one year after surgery, expanded with gold standard pathophysiological measurements for collapsibility. Two measurements will be performed during the DISE, one with HNS on and one with HNS off.	
Control	N/A	
	Objectives	**Outcome Measures**
Primary	To assess upper airway collapsibility with and without hypoglossal nerve stimulation (HNS) treatment during drug-induced sleep endoscopy (DISE) expanded with additional collapsibility measurements.	Collapsibility assessed during DISE with and without HNS, one year after surgery.
Secondary	Primary outcomes will be compared between responders and non-responders.	Collapsibility assessed during DISE with and without HNS, one year after surgery, specifically for responders and for non-responders.
Planned Sample Size	Accounting for a participant dropout of 10%, a total of 21 participants will be recruited in order to have an inclusion of 19 participants.	
Treatment duration	N/A	
Follow up duration	N/A. Patients will not have study-specfic followed-up after the study procedures, only standard clinical follow-up.	
Duration of the experiment (FPI-COV)	Two years. Participants will be included from December 1st, 2025, until November 30th, 2027. Study procedures will be performed until December 31st 2027.	

SCHEDULE OF ASSESSMENTS - FLOWCHART

Table 1: Schedule of assessments

	One-year follow-up consultation (standard clinical pathway)	*One-year follow-up PSG (standard clinical pathway)*	*One-year follow-up DISE with additional measurements*	*Discussion of results and end of study visit*
Acceptable windows	*N/A*	*Within 90 days after consultation*	*±30 days within one-year follow-up PSG*	*Within 60 days after one-year follow-up PSG*
Informed Consent	*X*			
Demographics	*X*			
Medical History	*X*			
Eligibility assessment	*X*			
Physical Examination	*X*			
Adverse events		*X*	*X*	*X*
Height, Weight and BMI	*X*	*X*		

[1]Blood pressure, heart rate, respiratory rate, and 12-lead electrocardiogram at pre-dose and 1 hour after administration, body temperature only at pre-dose. Blood pressure, heart rate, respiratory rate, and 12-lead electrocardiogram will be measured after 5 minutes rest in supine position. Accepted deviations for the 1 hour post-dose assessments are ±10 minutes.

[2]In case the subject is experiencing symptoms such as chest pain, shortness of breath, dizziness, fainting, or fast or irregular heartbeats (palpitations), the investigator will consider a 12-lead electrocardiogram.

1 PROTOCOL

1.1 BACKGROUND

Obstructive sleep apnea (OSA) is one of the most prevalent respiratory disorders and the most frequent type of sleep-disordered breathing, characterized by recurrent pharyngeal collapses during sleep. This disturbance results in fragmented, nonrestorative sleep.[1] Furthermore, intermittent hypoxemia might result in both acute and chronic elevation of blood pressure, while also being a risk factor for overall all-cause mortality.[2,3] OSA symptoms include snoring, unrefreshing sleep, fatigue, excessive sleepiness and nocturnal gasping or choking.[4] OSA is diagnosed using polysomnography (PSG), during which several parameters are measured throughout the night, including airflow, electroencephalography, electromyography, oxygen desaturation and heart rate. Using these measures, OSA severity is quantified by the apnea-hypopnea index, capturing the number of apneas and hypopneas per hour of sleep.

As OSA is associated with multiple comorbidities, efficient treatment is mandatory.[5] In clinical practice, the standard treatment for OSA is continuous positive airway pressure (CPAP), which opens the upper airway by creating a pneumatic splint.[6] Alternative treatments include mandibular advancement device (MAD) treatment, which (re)opens the upper airway by protruding the mandible, position treatment to avoid supine position, drug treatments, hypoglossal nerve stimulation treatment and other surgical treatments.[7-9] While CPAP is characterized by an overall greater efficacy, adherence might be limited. Non-CPAP treatments are characterized by a higher adherence, yet their efficacy is patient dependent.

Respiration-synchronized hypoglossal nerve stimulation (HNS) is an innovative technique in which the hypoglossal nerve is stimulated to protrude the tongue during inspiration.[10] While HNS has demonstrated clinical efficacy in treating OSA, its impact on the underlying pathophysiological mechanisms of OSA remains insufficiently understood. A lot of effort has been put in upfront patient selection of this treatment. Five pathophysiological parameters are known to be associated with OSA treatment outcome: site of collapse, upper airway collapsibility, ventilatory control instability, muscle responsiveness, and arousal threshold.[11] These key pathophysiological traits have also been shown to be associated with HNS treatment outcome.[12] Among these five key traits, only the site of collapse is routinely assessed in clinical practice using drug-induced sleep endoscopy (DISE), which has been proven to be associated with HNS treatment outcome.[13]

For the remaining four traits (collapsibility, ventilatory control instability, muscle responsiveness and arousal threshold) no standardized clinical techniques are currently available. The current gold standard technique to assess these traits is an overnight study with repeated pressure-drops.[14] Collapsibility is commonly assessed in research using the critical closing pressure (P_{crit}), where a higher P_{crit} indicates a more collapsible airway.[15] A recent paper by our research group described a technique to assess the P_{crit} during DISE procedures, using additional measurements with a modified nasal mask and modified CPAP device.[16]

1.2 RATIONALE

While the effectiveness of HNS has repeatedly been proven, the effect of HNS treatment on OSA-specific upper airway collapsibility is currently unknown. As such, measuring the P_{crit} during DISE could provide a direct physiological measure of airway stability and is particularly relevant for understanding the mechanical effects of HNS therapy. This study aims to assess the effect of HNS on upper airway collapsibility by measuring P_{crit} during DISE, both with and without stimulation. This knowledge will be important to improve our understanding of the treatment mechanisms of HNS and could eventually improve patient selection and personalized medicine.

1.3 ASSESSMENT AND MANAGEMENT OF RISK

The possible risks for the participants are the same as for patients undergoing a DISE procedure in current clinical practice. Risks include epistaxis (due to injury from the laryngoscope), laryngospasm and aspiration of saliva. Only little risk is added by the additional measurement of Pcrit, airflow, esophageal pressure and routine PSG measurements.

As such, this study is defined as a low-risk study.

1.4 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

1.4.1 Primary objective

To assess the effect of hypoglossal nerve stimulation (HNS) treatment on upper airway collapsibility (critical closing pressure, Pcrit). This ventilatory trait will be measured during drug-induced sleep endoscopy with additional measurements, at baseline and with HNS.

1.4.2 Secondary objectives

1. To compare these effects between responders and non-responders
2. To assess the relationship between changes in collapsibility and changes in DISE outcomes with HNS treatment.

1.4.3 Primary endpoint

Change in pharyngeal critical closing pressure (ΔPcrit), between DISE at baseline and DISE with HNS treatment

1.4.4 Secondary endpoints

1. ΔPcrit in responders and in non-responders; ΔAHI from baseline to one-year follow-up to measure treatment response
2. Δ%area-of-collapse at the level of the palate, tongue base, lateral walls and epiglottis, between baseline and DISE with HNS.

1.5 DESIGN

1.5.1 Description study design

Patients who undergo hypoglossal nerve stimulation therapy will be recruited at the one year follow-up appointment at the department of ENT. As part of the standard clinical pathway, these patients will have a PSG and DISE planned one year after HNS-therapy intiation. Participants of this study will be invited to to have their one year follow-up DISE extended with additional measurements to assess the effect of HNS therapy on upper airway collapsibility.

1.5.2 Duration

The inclusion of participants will be performed from December 1st, 2025, until November 30th, 2027.

1.5.3 Time schedule study

- December 2025 - November 2027
    - Inclusion of participants who received hypoglossal nerve stimulation therapy, at the clinics of the department of ENT at UZA.
    - Additional measurements for upper airway collapsibility during one year follow-up DISE

1.6 SETTING

Single centre study at Antwerp University Hospital, Edegem, Belgium.

1.7 PARTICIPANT ELIGIBILITY CRITERIA

We expect to implant 45 participants per year with HNS treatment. Therefore, we do not expect an issue to recruit 21 participants over a period of 2 years.

1.7.1 Inclusion criteria

Inclusion criteria for this research are:

- 18 years or older.
- Treated with HNS-therapy for OSA (AHI ≥15/hour sleep)
- Capable of giving informed consent
- Baseline polysomnography performed at Antwerp University Hospital

1.7.2 Exclusion criteria

Exclusion criteria for this research:

- Patients did not receive HNS-therapy at the Antwerp University Hospital
- Central apneas accounting for ≥25% of total apneas during baseline polysomnography
- Known medical history of intellectual disability, memory disorders or current psychiatric disorders (psychotic illness, major depression, or acute anxiety attacks as mentioned by the participant).
- Simultaneous use of other treatment modalities to treat OSA (outside of HNS-therapy)
- Esophageal ulceration, tumors, diverticulitis, bleeding varices, sinusitis, epistaxis, recent nasopharyngeal surgery
- Pregnancy or willing to become pregnant
- Excessive alcohol or drug use (> 20 alcohol units/week or any use of hard drugs)

1.8 PROCEDURES

1.8.1 Recruitment

Patients who undergo hypoglossal nerve stimulation therapy will be recruited at the one-year follow-up appointment at the department of ENT. Participants will be invited to have their one year follow-up DISE extended with additional measurements to assess upper airway collapsibility.

1.8.1.1 Patient identification

Patients will be identified by the project manager (ET) at the one-year follow-up appointment for HNS treatment.

1.8.1.2 Screening

All HNS patients scheduled for their 1-year follow-up will have their medical records screened and will be invited to participate in the study if eligible. All patients with HNS therapy will have received a baseline PSG as a requirement for HNS implantation.

1.8.2 Consent

The responsible doctor will introduce the study to the participants at the one-year follow-up consultation (see Table 1). When participants meet the inclusion criteria they will be asked to participate in the study. The decision regarding participation in the study, which is made by the participant, is entirely voluntary. Refusal of participation will have no consequences for further treatment of the participant. They will be asked to sign informed consent. (See appendix for participant information and informed consent).

Only patients capable of giving informed consent will be considered for inclusion. At each moment of time, participants will be allowed to ask questions regarding the study and participation. Participants will be given contact details (telephone number and e-mailaddress) on the informed consent form. At each moment of time, participants are allowed to step out of the study with no consequences for further treatment of the participants.

1.8.3 Baseline data

Baseline data will include standard clinical assessments that are part of the clinical pathway for HNS implantation and follow-up. These include the baseline full-night PSG, baseline DISE (both before implantation), one year follow-up full-night PSG and one year follow-up DISE. An additional one year follow-up DISE with additional measurements will be performed specifically as part of the study.

Data collected during the one year follow-up consultation:

- Demographics and complaints: year of birth, sex, weight, height, age and date of enrollment, ethnicity, OSA history (main complaint, other complaints, other concomitant sleep disorders, previous treatment)
- Data on the HNS implant: date of examination, type of implant, date of implantation, specific device settings (amplitude, voltage upper and lower limit, rate, pulse width, start delay, duration of stimulation, pause time, electrode configuration), direction and strength of tongue protrusion, mean therapy usage per week, additional remarks

Data of full-night PSGs (baseline and one year follow-up) will include:

- PSG measurement info: raw data, date, protocol used
- Anamnestic information: main and other reasons for the PSG, presence of sleepiness and/or tiredness, presence of apneas, presence of problems with sleeping in or sleeping through the night, Epworth sleepiness scale (ESS) and visual analogue scale (VAS) for snoring, usage of alcohol, smoking or caffein.
- Demographic data: age, sex, weight, length, neck circumference and abdominal circumference
- Sleep stages and architecture: Total sleep time and total sleep registration, proportion and duration of each sleep stage (N1, N2, N3 and REM), sleep latency (time to fall asleep), REM latency, number and duration of awakenings/arousals, and sleep efficiency.
- Respiratory events: Apneas (complete cessation of airflow), hypopneas (partial reduction in airflow), along with their frequency (apnea-hypopnea index, AHI), type (obstructive, central, or mixed), associated postions and sleep stages (events in specific sleep positions, events in REM and non-REM sleep), and information on oxygen saturation and desaturation (mean and minimal oxygen saturation, oxygen desaturation index or ODI) and associated parameters
- Arousal index: Number of arousals per hour, which can indicate sleep fragmentation, and whether these are more pronounced in specific sleep stages or positions.

- Movement events: Periodic limb movements and their index.
- Specific description of snoring and which sleep positions it is present.
- Abnormalities in electrocardiography (ECG) measurement
- Presence of other sleep characteristics: alpha-intrusion, alpha-delta sleep, Cheyne-stokes breathing, bruxism, additional remarks
- Raw data of PSG measurements

Data of DISE (baseline and one year follow-up) will include:

- Weight
- Measurements during each specific maneuver (baseline, non-supine, chin-lift, simulation bite if used): upper-airway collapse (site, pattern and degree) which is also video recorded and saved on a hard-drive disk, snoring
- Target-controlled infusion (TCI) minimum and maximum amount, bispectral (BIS) monitoring values, additional remarks.

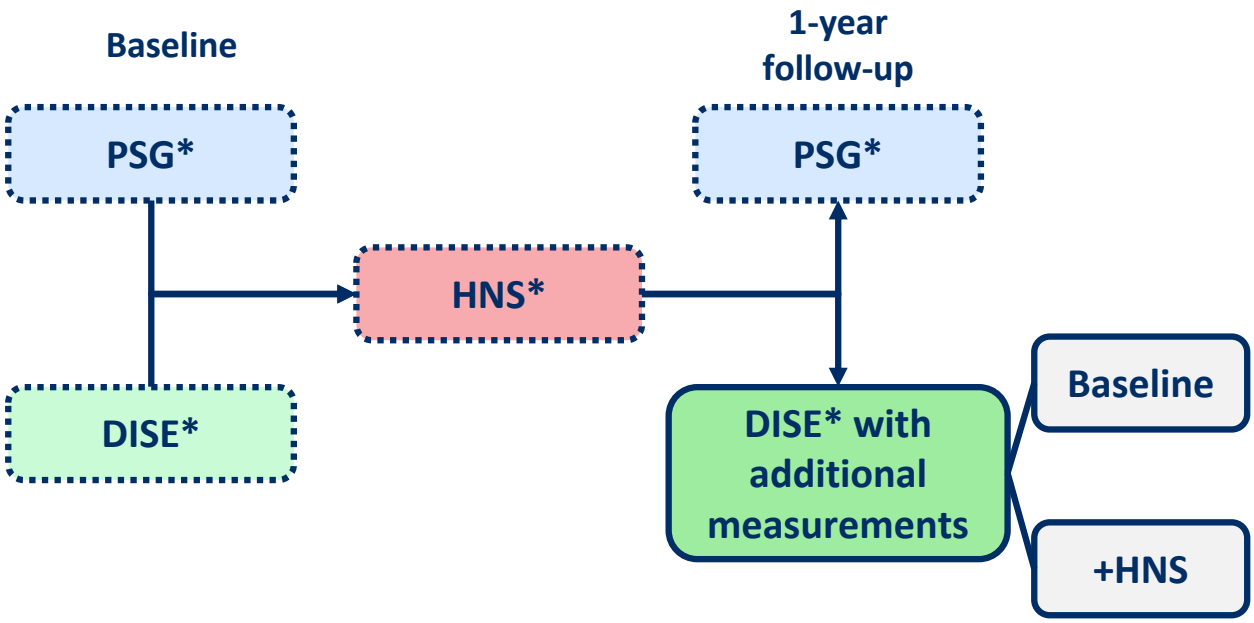
Additional measurements will be performed during the one year follow-up DISE:

- Type I PSG (Alice LDx 6, Philips Respironics) which includes: EEG, EOG, respiratory effort (respiratory inductance plethysmography, RIP) , SpO2 and chin EMG.
- Measurements of Pcrit (Pcrit3000 device, Philips Respironics)
- Airflow (Pneumotachometer, Hans-Rudolph, USA)
- Mask pressure (Differential pressure transducer)

Throughout the study, adverse events will be collected and reported.

1.8.4 Assessments

Patients treated with HNS-therapy for OSA will be invited to participate in the study. Data from the baseline PSG, baseline DISE, one year follow-up PSG and one-year follow-up DISE as part of the standard pathway for HNS-therapy will be accessed and collected. For this study, patients will have their one year follow-up DISE expanded with the measurement of airflow, EEG, EOG, respiratory effort, SpO_2 and chin EMG recorded through a Philips Alice LDx 6 system. An overview of the study procedures can be found in Figure 1.



**: part of the standard clinical pathway for hypoglossal nerve stimulation (HNS)*
DISE: drug-induced sleep endoscopy
PSG: polysomnography

Figure 1. Study procedures.

1.8.4.1 Polysomnography (PSG)

Baseline polysomnography (PSG) is part of the standard clinical pathway for HNS-eligibility in patients with OSA. Furthermore, a PSG at one-year follow-up is part of the standard follow-up pathway in patients receiving HNS-therapy.
In this study, PSG data will be collected from both baseline and one-year follow-up PSGs to assess treatment effect.

Furthermore, other endotypic parameters besides the passive Pcrit (active Pcrit, muscle responsiveness, loop gain, arousal threshold) will be calculated from raw PSG data using non-invasive endotyping measurements. The patient will not undergo additional tests for this.

1.8.4.2 Drug-induced sleep endoscopy (DISE)
Drug-induced sleep endoscopy (DISE) is the clinical standard diagnostic test to assess site, pattern and degree of upper-airway collapse in patients with OSA. For eligibility for HNS implantation in the standard clinical pathway, a DISE is a necessary tool for patient selection for this treatment. Furthermore, a DISE at one year follow-up is used in standard clinical practice to assess the effect of HGNS on the upper airway.
In this study, participants will have their DISE at one-year follow-up expanded with additional measurements to assess the effect of HNS-therapy on the collapsibility (see 1.8.4, 1.8.4.3 and Figure 2). The procedure will be performed in a semi-dark, silent operating theatre. Participants will lay in supine position. During the whole procedure, depth of sleep will be monitored using EEG-derived measurements. Sleep will be induced using 1.5 mg bolus injection midazolam and target-controlled propofol infusion (2.0 – 3.0 µg). The Pcrit measurement for collapsibilty will be performed (see 1.8.4, 1.8.4.3 and Figure 2) alongside, the standard DISE protocol: a flexible fiberoptic nasopharyngoscope (Olympus END-GP, 3.7 mm diameter, Olympus Europe GmbH, Hamburg, Germany) will be inserted through one of the nostrils into the transnasal cavity. Site, pattern and degree of collapse will be assessed using a standardized scoring system (Figure 1).
All DISE procedures will be scored by the same four experts in DISE from our research team, using consensus scoring based on the VOTE-classification (Figure 1) to avoid inter-rater variability.

1.8.4.3 Additional measurements
Besides the standard DISE, type I polysomnography (Alice LDx 6, Philips Respironics) expanded with measurements of Pcrit (Pcrit3000 device, Philips Respironics) and airflow (Pneumotachometer, Hans-Rudolph, USA) will be performed.

A nasopharyngeal mask will be used to measure Pcrit, which is connected to a pneumotachometer and the Pcrit3000 device. The mask pressure and airflow will be continuously recorded alongside standard PSG signals.
An overview of the set-up can be found in Figure 2.

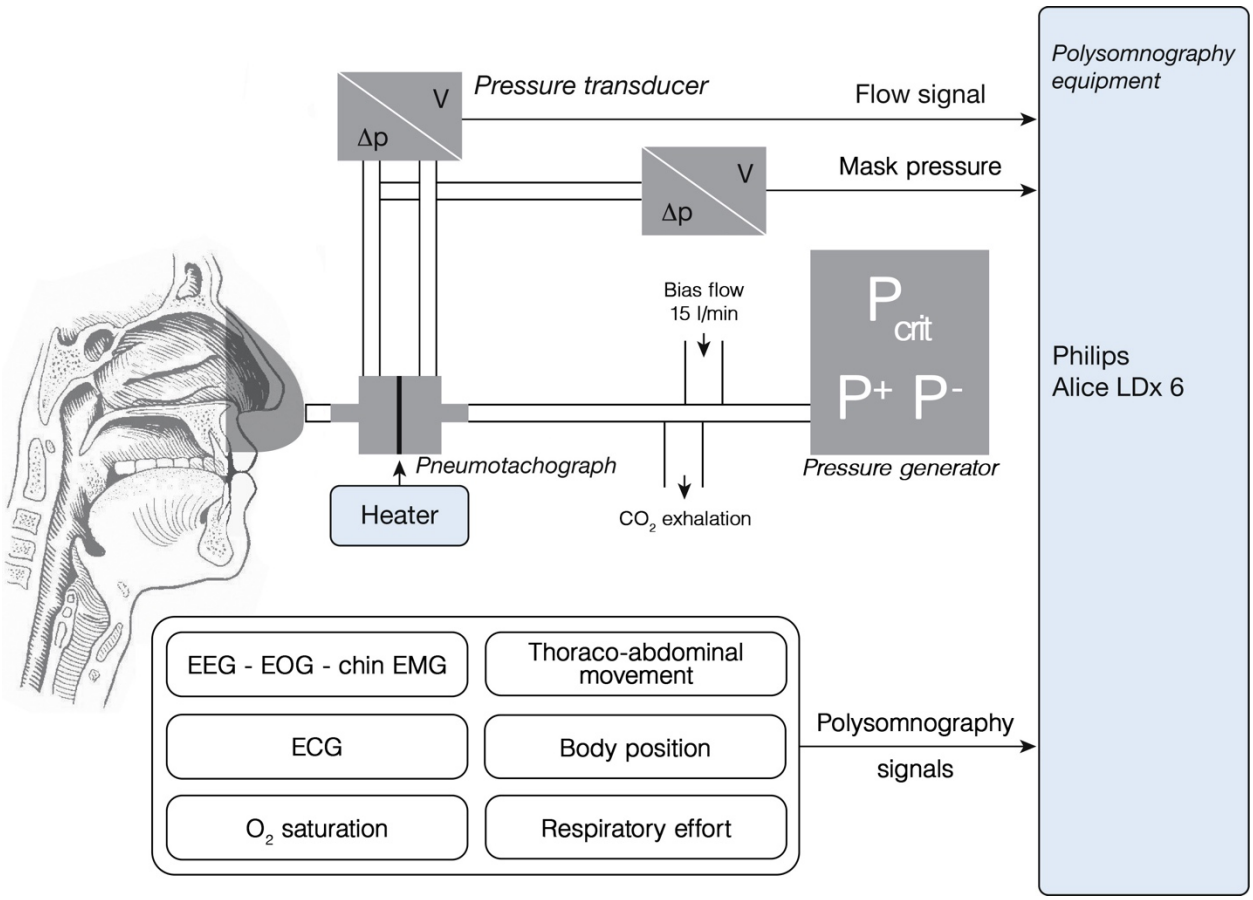


Figure 2. A generic set-up for the measurement of critical closing pressure (Pcrit). Airflow (V), pressure difference (ΔP), electrocardiography (ECG), electroencephalography (EEG), electromyography (EMG), Oxygen (O2), positive pressure (P+), and negative pressure (P−).[17]

Following sleep onset, as determined by EEG signals, CPAP will be titrated upward until flow limitation is eliminated. This pressure, referred to as the holding pressure, serves as the baseline for all subsequent measurements in each individual OSA patient.

For the measurement of the passive Pcrit (without compensatory muscle activity), once stable sleep is observed, the holding pressure will be abruptly reduced by 1 cmH_2O during expiration for five consecutive breaths. The pressure will then be returned to the holding level for one minute. This cycle will be repeated with incremental reductions of 1–2 cmH_2O for five breaths each time, until an obstructive apnea is observed—defined as a ≥90% reduction in airflow lasting at least 10 seconds.
If an arousal occurs during the procedure, the pressure will be reset to the holding level, and the measurement sequence will be repeated. Breaths associated with arousals will be excluded from the final analysis.

Alongside the Pcrit measurement, DISE will be performed as per standard clinical protocol.

1.8.5 Withdrawal criteria

1.8.5.1 Discontinuation of intervention

If the intervention (Pcrit measurement) is stopped early, the reason should be recorded in the patient's medical records and be reported on the appropriate (e)CRF whether it is due to either the patient's or clinician's decision. Reasons for stopping protocol intervention may include, but are not limited to:

- The patient does not wish to continue with further experimental intervention
- Safety reasons
- Other reason

1.8.5.2 Withdrawal of consent (discontinuation participation)

Participants can withdraw at any moment for any reason during the study without any consequences. Treatment of the participant will be continued in the usual matter according to medical standards. The researcher may also decide to withdraw the participant from the study for medical reasons.

For the purposes of this experiment, withdrawal is defined as:

- The patient would like to withdraw consent from experiment and is not willing to be followed up for the purposes of the experiment at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the analysis, no data can be collected anymore from this time point).

The details of withdrawal will be clearly documented in the patient's medical records and in the (e)CRF. When a participant withdraws from the study, normal medical treatment will be continued according to the standard clinical pathway.

No specific replacement of the individual participant will occur after withdrawal during the study, as all patients treated with HNS-therapy for a period of one year will be invited to participate in the study. Participant inclusion will continue until 19 participants have a full dataset. With an expected 10% drop-out, we aim to include 21 participants.

1.8.5.3 Loss to follow-up

If a patient is lost to follow-up before all procedures were performed for which data is collected during this study, every effort will be made to contact the patient.

1.8.5.4 Premature termination of the study

Premature termination of the study will take place when a participant experiences severe medical complaints or adverse events take place in which the participant is not able to continue the study (cardiovascular problems, trauma etc.). Before termination, the SC will be consulted.

1.9 INTERVENTION

1.9.1 Name and description of intervention(s)

As part of this study, participants will have their DISE procedure at one year follow-up expanded with additional measurements. The DISE procedure itself is a recognized procedure in Belgium and is indicated for patients with OSA looking for non-CPAP therapy options. In patients with HNS (which is a requirement for this study), a DISE with HNS at one year follow-up is part of the standard clinical pathway to assess the effect of HNS therapy on the site, pattern and degree of collapse during sleep.

The additional measurements will include measurements for Pcrit – using a Pcrit device – and measurements for airflow. Pcrit measurement will be performed during stable sleep under sedation, using repetitive pressure drops during expiration from the holding pressure. During this procedure, airflow and PSG signals will also be measured (see Figure 2 and 1.8.4.3 for more details).

1.9.2 Legal status of the intervention

The DISE procedure is a known and commonly used procedure in patients with OSA for non-CPAP therapy selection. This is a reimbursed procedure in Belgium. For this study, the DISE will be extended with additional measurements which will be carried out under an EC approval. This specific intervention is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

1.10 SAFETY RECORDING AND REPORTING

1.10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a clinical intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention.
Adverse Reaction (AR)	An untoward and unintended response in a participant to the intervention. The phrase "response to the intervention" means that a causal relationship between a intervention and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the intervention, based on the information provided.

1.10.2 Recording of safety findings in function of the available evidence

Only little risk is added by the additional measurement of Pcrit, airflow and routine PSG measurements during the DISE procedure.

1.10.2.1 Recording of adverse events

Florence eBinders will be used as the CRF for this study. All AEs and SAEs reported by the participant or observed by the investigator will be recorded in this CRF system.

1.10.2.2 Reporting of adverse events

The investigator will inform the participants and the Sponsor if a SAE occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the ethical committee, except when suspension would jeopardize the participants' health. The investigator will take care that all participants are kept informed.

All SAEs will be reported to the Sponsor within 15 days after the investigator has first knowledge of the serious adverse reactions.

1.10.2.3 Follow-up of adverse events and reactions

All adverse events and reactions will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

1.10.3 Responsibilities

Study-coordinator/trial manager and principal investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

- Using medical judgement in assigning seriousness, causality and expectedness.
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness.
- Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Sponsor:

- Central data collection and verification of AEs, SAEs according to the protocol onto a safety database.
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Preparing standard tables and other relevant information for the annual safety reporting in collaboration with the CI and ensuring timely submission to the EC.

1.10.4 Reporting urgent safety measures

If any urgent safety measures are taken the Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant EC of the measures taken and the circumstances giving rise to those measures.

1.11 STATISTICS AND DATA ANALYSIS

1.11.1 Sample size calculation

Sample size is based on previous research assessing the effect of MAD treatment on upper airway collapsibility, measured by pharyngeal critical pressure (P_{crit}).[18] Specifically, we used the change in Pcrit from baseline to suboptimal titration, which showed a mean decrease of 2.7 cmH_2O with a standard deviation of 3.8 cmH_2O. This estimate was chosen to avoid overestimating the effect size, as the optimal titration phase would have yielded a larger effect and potentially underestimated the required sample size. Taking into account a desired power of 80%, at least 19 patients should be included in this protocol. Accounting for a drop-out rate of 10%, a total of 21 patients will be recruited for this study.

1.11.2 Planned recruitment rate

We expect to implant 45 participants per year with HNS treatment. Therefore, we do not expect an issue to recruit 21 participants over a period of 2 years.

1.11.3 Statistical analysis plan

1.11.3.1 Summary of baseline data and flow of patients

Descriptive analyses will be performed for all assessments. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage. Confidence intervals will be provided where relevant. The confidence level will be 95%, unless specified otherwise. Baseline value will be defined as the last valid value prior to the implant procedure.

1.11.3.2 Primary outcome analyses

The following analyses will be performed:

- Descriptive statistics will be performed to visualize an overall change in P_{crit} using the results from one year follow-up DISE without and with HNS in all participants.
- Normality will be tested for the P_{crit} in all participant.s
- Effect of HNS on collapsibility will be tested using paired test – either paired t-test or Wilcoxon signed-ranked test.

1.11.3.3 Secondary outcome analyses

The amount of collapse on palatal, oropharyngeal, tongue base and epiglottic level will be scored in a quantitative way using ImageJ, which will result in %area-of-collapse with and without HNS stimulation. Participants will be divided in either the “responder” group or the “non-responder” group, based on several definitions as reported in literature, including the Sher15-criteria for Surgical success in which there should be a final AHI of ≤15 and a final AHI reduction of ≥50% at 1-year follow-up.[19,20] Additionally, there should be a mean usage of at least 4 hours a day for surgical response.

Based on these calculations, the following analyses will be performed:

- Descriptive statistics will be performed to visualize an overall change in AHI and Δ%area-of-collapse, using the results from the PSG at baseline and follpw-up, and the one year follow-up DISE without and with HNS in all participants.
- Normality will be tested for the AHI in all participants and specifically for responders and non-responders.
- Difference in improvement in collapsibility between responders and non-responders will be tested using either unpaired t-test or Mann-Whitney U test.
- Regression analysis will be performed to assess association between ΔP_{crit} and treatment response.
- Correlation and regression analyses will be used to assess associations between improvement in collapsibility (increased ΔP_{crit}) and reduction in %area-of-collapse at each level of the upper airway.

1.11.3.4 Procedure(s) to account for missing or spurious data

Missing data for the different endpoints will not be replaced and will thus not be taken into account in the analysis.

1.12 DATA HANDLING

1.12.1 Data collection tools and source document identification

Data	ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."
Source Documents	ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."
Electronic Case Report forms	An electronic case report form ((e)CRF) system will be used by all participating sites to collect the individual patient data required by the trial protocol. There are three primary sources for the collection of trial data. For data collected during routine clinical visits (clinical findings, observations, laboratory data, etc.), the participating site's (electronic) medical record will be used as a primary source. The (e)CRF system will be the primary source for questionnaire and treatment report data collected electronically per the subject's email address. For subjects that were unable to complete the questionnaires and treatment report electronically, the paper questionnaires and treatment report will be the primary source. The (e)CRF data will be used to perform the statistical analyses for the trial, as described in Section 11.3.

The (e)CRF system will not be used as a primary source of data, except experiment related questionnaires that were completed electronically per email by the patient.

More details on data handling can be found in the Datamanagement Plan.

1.12.2 Archiving

Regarding the archiving period of data of experiments according the Belgian law of May 7th 2004 regarding experiments on humans: both digital files and paper files must be kept 20 years after completion of the experiment.
Patient (hospital) files will be archived for 30 years.

The institution/investigator shall archive the investigator site file ("ISF") at the institution using an electronic investigator site file binder solution specified by the Sponsor ("eISF Solution"). The ISF shall include all "Essential Documents", which are all documents as required by applicable laws, including in particular all documents relating to the study which allow evaluation and verification of the conduct of the study and the quality of the data generated. The institution and the investigator will be responsible for uploading and updating all Essential Documents in the ISF and the eISF Solution, in accordance with applicable laws. To the extent institution/investigator is required by applicable laws to upload and/or update Essential Documents and/or other data in the ISF/eISF Solution that would allow Sponsor to identify study subjects, institution/investigator may only do so in designated folders with proper protection, with Sponsor having no access to such folders. Institution/investigator may not upload any Essential Documents or other data into the ISF/eISF Solution in a manner that would allow Sponsor to identify study subjects.

1.13 MONITORING, AUDIT & INSPECTION

Before initiation, at a site initiation visit a representative from the Sponsor will review the protocol and data capture requirements (i.e. (e)CRFs) with the local investigators and their staff. During the experiment, field monitors employed by the Sponsor (belonging to the CTC) will employ several methods of ensuring protocol and Good Clinical Practice compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture and data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrolment, and to ensure that treatment is being dispensed and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by the centralized Sponsor research associate (CRA).

The investigator must maintain source documents for each patient in the experiment, consisting of case and visit notes (hospital medical records) containing demographic and medical information, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. The investigators must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to a study-specific monitoring plan. This monitoring plan will be approved by CI. The monitoring visits including site initiation visit and close out visit will be performed at each site. Within a period of a month, if there is no on-site monitoring visit, a remote monitoring visit will be performed according to the monitoring plan. Any significant deviation from the planned monitoring timelines will be explained and documented in the monitoring report. If necessary, an amendment of the monitoring plan will be drawn up and approved again by CI.

If sites (fertility centres) do not register patients or stop enrolment, no regular monitoring visit will be planned. In the case of long-term absence (more than 4 months) of research activities, the monitor will ensure the research team is adequately trained when the research activity is restarted.

No information about the identity of the patients will be disclosed in the (e)CRF.

1.14 ETHICAL AND REGULATORY CONSIDERATIONS

1.14.1 Regulatory review & reports

Prior to including patients in the registry, approval will be sought from the regulatory authorities and Ethical Committee (EC) for the protocol, informed consent forms and other relevant documents. Substantial amendments that require review by EC will not be implemented until the EC grants a

favourable opinion for the experiment. All correspondence with the EC will be retained in the Trial Master File/Investigator Site File. An annual progress report will be submitted to the EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

- it is the SC responsibility to produce the annual reports as required.
- the SC will notify the EC of the end of the experiment
- if the experiment is ended prematurely, the SC will notify the EC, including the reasons for the premature termination
- within one year after the end of the experiment, the SC will submit a final report with the results and a lay summary, including any publications/abstracts, to the EC

1.14.2 Peer review

The final summary of this proposal was sent to all candidate participating centres for further review, commenting and discussion. A PI investigators meeting was organised to have discussion and approval on in- and exclusion criteria as well as on the procedure. The current version of the full proposal is therefore based on the comments expressed by the candidate centres. In addition, this proposal was discussed with one international expert on tubal patency testing and clinical aspects of infertility in general .
Peer review has been independent, expert, and proportionate:

- Expert: The above-mentioned reviewers have knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol and have the expertise to assess the methodological aspects of the experiment.
- Proportionate: Peer review is considered to be commensurate with the size and complexity of the experiment. This multicenter experiment requested a higher level of peer review (more reviewers with broader expertise and often independent review committee or board), and international peer review.

1.14.3 Public and Patient Involvement

There will be no public and patient involvement in this study.

1.14.4 Regulatory Compliance

The trial conduct will comply with any and all applicable laws and local requirements, including but not limited to

- the International Conference on Harmonisation Guidelines (ICH Guidelines),
- the Belgian law of May 7th 2004 regarding experiments on humans

In accordance with the aforesaid applicable laws, regulations and guidelines, the trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from regulatory.

1.14.5 Protocol compliance

The trial will be carried out in full compliance with the final version of the protocol. Waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

All protocol deviations that occur during the protocol which are related to a patient will be documented in the patient file (medical record) and (e)CRF. The (e)CRF deviation log will capture the deviation description, deviation type, deviation date, date identified, relation to adverse event. If a protocol deviation is related to more than one patient this deviation must be recorded in the (e)CRF of each patient. General protocol deviations will be recorded on a protocol deviation log and will be present in (e)ISF and (e)TMF. The sponsor will have to score all the deviations (major and minor). In case the deviation is scored major a corrective action should be started.

1.14.6 Data protection and patient confidentiality

Confidentiality will be maintained and as will the manner of how the trial is compliant with the requirements of the Belgian and European Privacy legislation (https://www.dataprotectionauthority.be/legislation-and-standards). All investigators and trial site staff must comply with the requirements of the above legislation on the protection of privacy in relation to the processing of personal data, with regards to collection, storage, processing, and disclosure of personal information.

Personal information collected at the trial site will be maintained and kept secure by the PI. Data entered into the trial software will be coded and depersonalised.

The data and linking code will be kept in separate locations using encrypted and password protected digital files. Access to these data will be limited to only those who need it for the purposes of quality control, audit, and analysis.

1.14.7 Access to the final trial dataset by other parties

Data will not be accessed by other parties.

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