EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

HYPOGLOSSAL NERVE STIMULATION SYSTEMS FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA

PROJECT ID: OTCA21

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Disclaimer

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Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form, which was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
AHI	Apnea-Hypopnea Index
APAP	Auto-Adjusting Positive Airway Pressure
ARTG	Australian Register of Therapeutic Goods
ASP	Average Sleep Propensity
BiPAP	Bi-level pressure
BMI	BODY MASS INDEX
BPAP	Bilevel positive airway pressure
CAI	Central apnea index
CG-I	Clinical global impression–improvement
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CUR	Current use of technology domain
DGSM	German Society for Sleep Research and Sleep Medicine
DOICU	Declaration of Interest and Confidentiality Undertaking
DRG	Diagnosis-Related Group
EFF	Effectiveness
ESS	Epworth Sleepiness Scale
FDA	U.S. Food and Drug Administration
FOSQ	Functional Outcomes of Sleep Questionnaire
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HGNS	Hypoglossal nerve stimulation
HRQoL	Health-Related Quality of Life
ICD	International Classification of Diseases
IHE	Institute of Health Economics
LAUP	Laser-assisted uvuloplasty
MA	Meta-analysis
MAH	Marketing Authorisation Holder
MeSH	Medical Subject Headings
MRI	Magnetic resonance imaging
NUB	New examination and treatment methods
ODI	Oxygen Desaturation Index
OR	Odds Ratio

OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PICO	Population-Intervention-Comparison-Outcome
PROM	Patient-Reported Outcome Measures
PSG	Polysomnography
QOL	Quality of life
RCC	Remote Control and Charger
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
RF	Radiofrequency Volumetric Reduction
RoB-2	Revised Cochrane risk-of-bias tool for randomized trials
RR	Relative Risk
SAF	Safety
SAQLI	Sleep apnea quality of life index
SR	Systematic Review
SE	Standard Error
TEC	Technical Characteristics of Technology Domain
UAS	Upper airway stimulation
UPPP	Uvulopharyngopalatoplasty

SUMMARY OF RELATIVE EFFECTIVENESS OF HYPOGLOSSAL NERVE STIMULATION SYSTEMS FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA

Scope

The scope can be found here: Scope.

It is hypothesized that the use of Hypoglossal Nerve Stimulation (HGNS) is more effective and safer than no treatment in those adult patients with moderate-to-severe obstructive sleep apnea (OSA) who present inadequate adherence to positive airway pressure systems or to other non-invasive procedures.

Introduction

Health problem, description of the technology and comparators

Obstructive sleep apnea (OSA) is a potentially serious sleep disorder in which breathing repeatedly stops and starts during sleep. It results from an upper airway collapse during sleep that occurs due to inadequate motor tone of the tongue and/or airway dilator muscles and is associated with intermittent hypoxia and transient arousals. Collapsibility can also be heightened by underlying anatomic problems. Obesity, and particularly central adiposity, both potent risk factors for sleep apnea, can increase pharyngeal collapsibility through mechanical effects on the pharyngeal soft tissues. Polysomnography performed in a sleep laboratory is the gold standard method for diagnosing OSA (B0001).

Continuous Positive Airway Pressure (CPAP) is considered the therapy of choice for moderate-to-severe OSA. Its clinical use can be compromised by poor compliance and some long-term complications. The population of interest for this assessment consists of patients with inadequate adherence or those who failed to respond to positive pressure systems or other non-invasive procedures. Inadequate adherence is defined as when a patient was unable or unwilling to use CPAP. In the US and Europe, CPAP intolerance is defined as: 1) an inability to tolerate CPAP greater than 5 nights per week (usage defined as greater than 4 hours per night), or 2) an unwillingness to use CPAP; for example, a patient returns the CPAP system after attempting to use it or experiences claustrophobia with repeated use (A0020).

An alternative for such patients is HGNS. Although conventional palate and tongue surgery to correct obstructions in the upper airway may be appropriate in selected patients, invasive surgical approaches to anatomical restructuring are not relevant comparators to HGNS, as these procedures do not address the underlying pathophysiology in OSA, the collapsibility of the upper airway musculature (B0002).

There are three HGNS products available for use in Europe: the Inspire® Upper Airway Stimulation (UAS) System (Inspire Medical Systems, Inc.), the aura6000™ System (ImThera Medical, Inc.) and Nyxoah's Genio™ system. In addition, there is a product that is no longer available [HNS/HGNS® System* (Apnex Medical, Inc.)] (B0004).

Methods

A systematic literature search in PubMed, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database for Systematic Reviews, as well as a manual search, was performed according to a predefined search strategy. The search was closed on January 20th

2020. The search identified 2,364 references. The final selection for qualitative analysis consisted of 8 articles. Quality assessment was carried out using the risk of bias tool RoB-2 for comparatives and the Institute of Health Economics tool IHE-20 for single-arm studies. The quality of the body of evidence was assessed using GRADE. A semi-structured interview of a patient was done during the scoping process.

Results

Available evidence

Only one comparative study that sought to assess effectiveness was identified, a randomized controlled therapy withdrawal study on the use of the Inspire® Upper Airway Stimulation System (UAS) (Inspire Medical Systems, Inc.). The authors reported data on effectiveness, but not on safety. Another six studies were selected to assess safety and adherence, all prospective single-arm studies. Those studies examined not only Inspire®, but also the following: the aura6000™ System, Apnex and Nyxoah's Genio™.

The quality of the evidence was very low, both for effectiveness and safety.

Clinical effectiveness

The only comparative study selected was a randomized withdrawal study involving the Inspire® Upper Airway Stimulation System (UAS). In this study, 46 patients successfully treated with UAS were randomized to have their device set to ON or OFF during a 1-week period. In this setting, an enrichment strategy was applied by including only responders to UAS therapy. Thus, a selection bias appeared, which affected the results.

The study found significant worsening in the Apnea Hypopnea Index (AHI) and the Oxygen Desaturation Index (ODI) when the device was disconnected for one week (mean difference of change between ON-OFF for AHI of 16.4 (9.2, 23.7 CI 95%, *P* value <.001); and for ODI of 15.4 (8.7, 22.1 CI 95%, *P* value <.001)) (D0005).

Significant differences were also found in Hypoxemia Time (percentage total sleep time with oxygen saturation < 90%). When the device was disconnected, the mean difference of change between ON-OFF was of 5.4 (0.1, 10.7 CI 95%, *P* value of 0.04) (D0005).

Regarding quality of life, there was a significant worsening after one week with the device deactivated group compared to the device activated group in ESS (Epworth Sleepiness Scale) and FOSQ (Functional Outcomes of Sleep Questionnaire) scores; mean difference of change between ON-OFF for ESS of 4.2 (2.0, 6.4 CI 95%, *P* value <.001); and for FOSQ of –2.3 (–3.8, –0.9 CI 95%, *P* value of 0.001) (D0013).

Neither the RCT nor the observational single-arm studies reported any deaths related to the procedure or device.

Although no comparative evidence was found regarding adherence, the largest single-arm study found a median use of the device of 5.7 hours per night in 382 patients after 12 months of follow-up (D0017).

No evidence was found regarding the following critical outcomes: cardio/cerebrovascular morbidity and long-term effects on quality of life (D0005, D0012).

Safety

No comparative evidence allows for ascertaining whether HGNS is safer than no treatment in the population of interest. However, information from prospective single-arm studies was retrieved and analysed (C0008).

A significant number of adverse events was reported, related both to the device and the procedure. An average of 1.02 adverse events per patient was reported and 3.45% of patients suffered a serious adverse event. The most frequent serious adverse events were surgical interventions due to replacement and repositioning or explantation of the device. The most frequent non-serious adverse event was discomfort/pain associated with device (C0008).

Patient involvement

As patient input was deemed relevant for the scoping phase, their experiences living with the disease and even with the device under evaluation were collected and discussed during the scoping phase, including the scoping meeting, with the assessment team and the clinical experts.

Upcoming evidence

NCT04031040 (EliSA). Single-arm study using Nyxoah's Genio™ with an estimated completion date of October 2023.

NCT03868618 (DREAM). Single-arm study using Nyxoah's Genio™ with an estimated completion date of June 2022.

NCT03763682 (BETTER SLEEP). Single-arm study using Nyxoah's Genio™ with an estimated completion date of January 2020, though no results have been reported as of yet. Inquiries to manufacturers seeking information were not successful.

NCT03844295 (AIRSTIM). Randomized withdrawal study using Inspire® with an estimated completion date of March 2020, though no results have been reported as of yet. No results have been provided by the manufacturer.

NCT03760328 (EFFECT). Randomized crossover study with Inspire® comparing it with sham stimulation. Estimated completion date June 2020.

NCT02413970. Single-arm study using Inspire® with an estimated completion date of December 2021.

NCT02263859 (THN3). Randomized parallel assignment open-label intervention trial using ImThera aura6000™ with an estimated completion date of December 2022.

Table 0-1: Summary of findings table of HGNS. Effectiveness

Outcome	Absolute Change after a week (mean ± SE)		Relative Difference of change ON – OFF (95% CI)	Number of participants (studies)	Quality
	HGNS ON	HGNS OFF			
Apnea Hypopnea Index	1.7 ± 6.4	18.2 ± 15.6	16.4 (9.2- 23.7) P value < .001	46 (1)	Very low
Oxygen Desaturation Index	1.6 ± 5.8	17.0 ± 14.5	15.4 (8.7- 22.1) P value <.001	46 (1)	Very low
Hypoxemia Time (HT)	-1.0 ± 6.4	6.5 ± 10.8	5.4 (0.1, 10.7) P value .04	46 (1)	Very low
FOSQ	0.0 ± 1.0	-2.3 ± 3.0	-2.3 (-3.8, -0.9) P value .001	46 (1)	Very low
ESS	-0.3 ± 1.8	3.8 ± 4.6	4.2 (2.0, 6.4) P value < .001	46 (1)	Very low

Abbreviations: HGNS: hypoglossal nerve stimulation; HT: percentage total sleep time with oxygen saturation < 90%; FOSQ: Functional Outcomes of Sleep Questionnaire; ESS: Epworth Sleepiness Scale

Table 0-2: Summary of findings table of HGNS. Safety

Outcome	Absolute Number of events (events per patient)	Number of participants (studies)	Quality
Serious device-related AEs (1st year)	9 (0.01)	868 (5)	Very low
Serious procedure-related AEs (1st year)	15 (0.02)	868 (5)	Very low
Serious device-related AEs (subsequent years)	11 (0.07)	157 (2)	Very low

Abbreviations: AEs: adverse events

1 SCOPE

Description	Project Scope
Population	**Adult patients with moderate-to-severe Obstructive Sleep Apnea (OSA) who presented inadequate adherence* or failure to positive airway pressure (PAP) systems or to other non-invasive procedures.** • ICD10: G47.3: Sleep apnea, G47.33: Obstructive sleep apnea (adult) • MeSH terms: Sleep Apnea, Obstructive or Obstructive Sleep Apnea * Patient was unable or unwilling to use CPAP. In the US and Europe, CPAP intolerance is defined as: 1) an inability to use CPAP more than 5 nights per week of usage (usage defined as more than 4 hours per night); or 2) an unwillingness to use CPAP; for example, a patient returns the CPAP system after attempting to use it or experiences claustrophobia with repeated use.
Intervention	**Surgical implantation of Hypoglossal Nerve Stimulation.** Other Names: • Upper airway stimulation • Targeted hypoglossal nerve stimulation MeSH terms: Implantable neurostimulators: E07.305.250.319.381; E07.695.202.381 Electric Stimulation Therapy: E02.331 E02.779.468; E02.831.535.468 Products/manufacturers: Inspire™ Upper Airway Stimulation device (Inspire Medical Systems, Inc., Maple Grove, MN); aura6000™ System (ImThera Medical, Inc., San Diego, CA/LivaNova); Nyxoah Genio™ System (Nyxoah SA, Mont-Saint-Guibert, Belgium)
Comparison	**No treatment** Rationale: Continuous Positive Airway Pressure (CPAP) is considered the therapy of choice for moderate-to-severe OSA. Its clinical use can be compromised by poor compliance and certain long-term complications. Only patients who present inadequate adherence or failure to positive pressure systems were the target group for the intervention [1,2]. A variety of oral appliances are used to treat patients with OSA, designed to achieve downward rotation or advancement of the mandible. Design variations include use of clasps, restricted elastic bands, or pressure tubes to open the airway [3]. Surgery to correct obstructions in the upper airway (resection of the uvula and soft palate, advancement of the tongue and other otorhinolaryngologic surgical procedures) may be appropriate for selected patients. Invasive surgical approaches to anatomical restructuring are not relevant comparators to HGNS, as these procedures do not address the underlying pathophysiology in OSA, the collapsibility of the upper airway musculature [4,5].
Outcomes	<u>Effectiveness</u> • Apnea-Hypopnea Index (AHI)*, • Oxygen Desaturation Index (ODI)**, • Percentage of sleep time with the oxygen saturation level below 90% • Epworth Sleepiness Scale (ESS)*** • Quality of life (Functional Outcomes of Sleep Questionnaire FOSQ, other generic or specific QOL measures) • Technical and Procedural Success • Rate of cardiovascular events • Rate of cerebrovascular events • Overall mortality • Adherence to treatment * Apnea–Hypopnea Index (AHI) is an index used to indicate the severity of sleep apnea. It is represented by the number of apnea and hypopnea events per hour of sleep. The apneas (pauses in breathing) must last for at least 10 seconds and be associated with a decrease in blood oxygenation. A reduction of at least 50% from baseline in the AHI score and/or an AHI score of less than 20 events per hour are suggested measures for indicating a response to treatment. ** The oxygen desaturation index (ODI) is the number of times per hour of sleep that the blood's oxygen levels drop by a certain degree from baseline. Combining AHI and oxygen desaturation gives an overall sleep apnea severity score that evaluates both the number of sleep disruptions and the

	degree of oxygen desaturation (low oxygen level in the blood). Moderate sleep apnea: 15≤AHI<30; Severe sleep apnea: AHI≥30. *** The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their likelihood of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The higher the ESS score, the higher that person's average sleep propensity in daily life (ASP), or their 'daytime sleepiness'. Safety All adverse events and serious adverse events (related or unrelated to the device or intervention): • Procedure-related complications • Device-related adverse events • Other serious adverse events Rationale: Included main outcomes already described in the Instructions for Use, STAR trial and ADHERE registry [6,7].
Study design	Effectiveness: Randomized clinical trials (RCTs), prospective non-randomized controlled studies, and other observational comparative studies. Safety: Randomized clinical trials, prospective non-randomized controlled studies, other observational comparative and non-comparative studies, and single-arm studies with > 10 patients.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

Distribution of the responsibilities and workload between authors and co-authors was as follows:

AETS-ISCIII:

- Developed first draft of EUnetHTA project plan and amended the draft when necessary.
- Performed the literature search.
- Carried out the assessment: answered assessment elements (Production of EFF and SAF domains), completed checklist regarding potential "ethical, organisational, patient and social and legal aspects" of the HTA Core Model R for rapid REA.
- Supported the production of all domains and quality checked the steps during production (data, information, sources).
- Sent "draft versions" to reviewers, compiled feedback from reviewers and carried out changes according to the reviewers' comments.
- Prepared final assessment and wrote a final summary of the assessment.

NSPHMPDB:

- Reviewed the project plan draft.
- Carried out the assessment: answered assessment elements (Production of CUR and TEC domains).
- Supported the production of all domains and quality checked the steps during their production (data, information, sources).
- Contributed to answering questions related to potential ethical, organisational, patient, social, and legal aspects.

Assessment team approved the final conclusions, as well as all draft versions and the final assessment, including the executive summary.

2.2 Source of assessment elements

The selection of assessment elements was based on the HTA Core Model Application for Rapid REA Assessments (4.2) [8]. The selected issues (generic questions) were transformed into actual research questions (answerable questions).

Please note that in some instances multiple research questions were answered in summary fashion; that is, these questions might be listed below one another, with a single answer subsequently addressing them all.

2.3 Search

For Effectiveness (EFF) and Safety (SAF) domains, we performed a systematic literature search in the bibliographic databases PubMed, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database for Systematic Reviews, according to the predefined search strategy. Furthermore, a search in the clinical trials registry ClinicalTrials.gov was carried out for ongoing studies. In addition to the electronic search, a manual search (see reference lists of relevant studies), as well as an Internet search, including guidelines, databases GIN (Guidelines International Network), and HTA agency websites, was performed. Moreover, a search of regulatory documents was also carried out at the U.S. Food and Drug Administration (FDA) website.

For the identification of studies, different search strategies adapted to each database were designed, combined with controlled terms (MeSH and EMTREE) and free text for indications (Sleep Apnea, Obstructive Sleep Apnea, Upper Airway Resistance Syndrome) and interventions (Upper Airway Stimulation, Implantable Neurostimulators, Electric Stimulation Therapy).

Inclusion and exclusion criteria were based on the PICO-question (see section 1 scope).

First search: 9/01/2020. Second search: 20/01/2020.

Medline Elsevier: First search, 527 results; Second search, 6 new results.

EMBASE: First search, 936 results; Second search, 29 new results.

CENTRAL (Cochrane): First search, 857 results; Second search, no new results.

A two-step process for validating the search strategies followed: validation sets for Medline and EMBASE search strategies and the PRESS Peer review tool for Medline search strategies [9] were conducted by an information specialist at the Servicio de Evaluación del Servicio Canario de la Salud – Fundación Canaria Instituto de Investigación Sanitaria de Canarias (SESCS-FIISC) .

In order to avoid patient overlap and to reinforce the identification and exclusion of duplicate publications, if the same institution had published sequential studies, the study with the highest number of cases was chosen. A reference managing software was used (EndNote X8) to manage references and remove duplicates.

Information to more fully describe the technical characteristics of the technology (TEC) and current use (CUR) domains were obtained from the relevant literature identified from the accessed databases in the systematic search, clinical guideline sites, and manual searches, including searches of manufacturer websites.

We used information submitted by the manufacturer for the TEC and CUR domains.

A survey of EUnetHTA partners was carried out in January 2020 to obtain information not only on the use of HGNS, but also on reimbursement issues related to the CUR domain.

Detailed tables on the search strategies can be found in Documentation of the Search Strategies Appendix 1.

2.4 Study selection

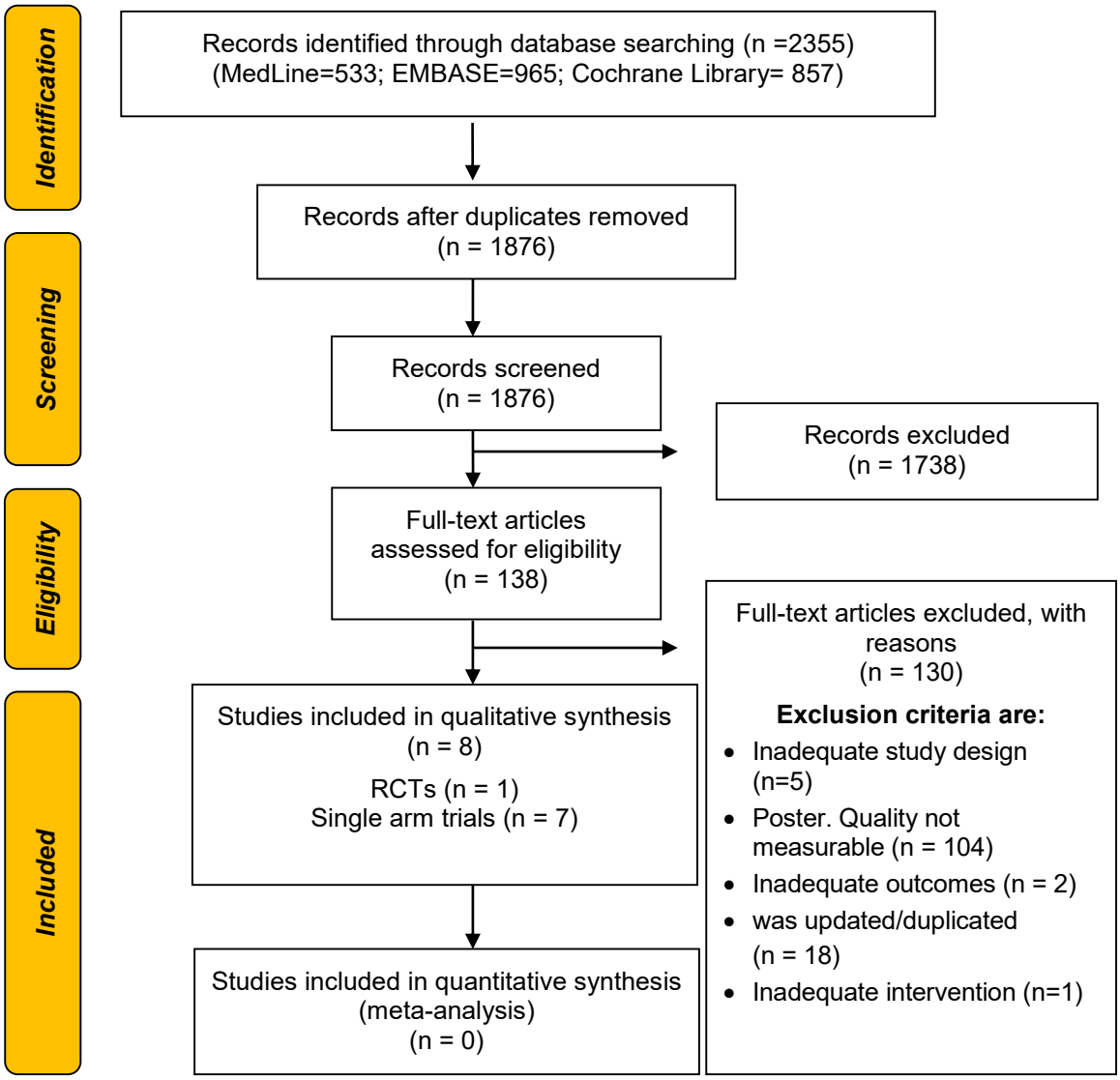


Figure 1: Flow chart

Systematic literature searches of bibliographic databases yielded 2,355 citations after the first and second (updated) searches. Eight additional references for guidelines and health technology assessments were identified through the search of study registries. After removing all duplicates, 1.876 references remained. Two researchers independently screened the 1,876 citations for eligibility. In cases of disagreement, a third researcher participated to resolve the situation. In the first step, 1,738 citations were excluded based on their titles and abstracts; in the second step, 130 of the remaining 138 articles were excluded after reviewing the full texts. This left 8 articles that met the inclusion criteria, of which 1 was a comparative study and 7 were case series. Manual searches of the reference lists of the included studies, topic-related systematic and non-systematic reviews, and queries to the device manufacturers resulted in no additional relevant studies (see Table A1 and Table A2 in Appendix 1).

2.5 Data extraction and analyses

Two review authors independently examined the extracted data using prepared data extraction sheets. The authors resolved any discrepancies through discussion with a third author. Data extracted from the studies included the following: information about the study (authors, year of publication, setting/country, funding, study design, clinical trial identification number/registry identifier and funding source). Participant/patient characteristics included diagnosis, number of participants in the trial, ages, clinical stage, and any relevant risk categories or risk factors. Intervention and control characteristics included a description of procedure, emergency/elective setting, comparator, name/type of the device, frequency of interventions per patient, length of follow-up and loss of follow-up. Outcomes for EFF and SAF domains were classified (critical, important, non-important) according to a previously used GRADE rating process shared among the Assessment Team (author(s), co-authoring team, dedicated reviewers) and the clinical experts [0]. A separate process to identify overlapping or repetitive data for any outcome from those trials with more than one publication was conducted. Queries sent to manufacturers and authors of the trials to determine the existence of results unpublished or in-press articles returned no further results.

Data were not summarized in a meta-analysis, as there was not sufficient homogeneity among the outcomes to allow for such analysis. For safety outcomes, the data were separated by serious and non-serious adverse events based on international standards. Thus, they were considered serious when they resulted in death, were life-threatening, required hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, or constituted a birth defect [11]. When there was scant information, we adopted the classification provided in the trials. The safety outcomes were grouped into 2 different follow-up periods: 6 to 12 months and 12 to 60 months.

2.6 Quality rating

For the TEC and CUR domains, no quality assessment tool was used. However, multiple sources were utilized to validate various individual, possibly biased, sources. A descriptive analysis of the different information sources was performed.

For EFF and SAF domains, we applied EUnetHTA guidelines in selecting quality-rating tools. The risk of bias at the study level was assessed using the Rob–2 for comparative studies [12] and the Institute of Health Economics (IHE-20) [13] checklist for single-arm studies (case series).

The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [10]. Disagreements were resolved by consensus.

2.7 Patient involvement

Patient involvement was pursued during the scoping phase. Patient feedback within the population target, including those using the device, was sought via clinical experts and organisations. The summary of answers validated by the patients and their feedback about the process culminated in interviews with the individual patients. After several contacts with individuals and organisations representing patients, only one patient agreed to participate in the assessment. A verbal informed consent was obtained before carrying out the telephone interview. Eventually, the patient signed a declaration of interest and confidentiality undertaking form (DOICU). The process to obtain patient input was “one-on-one conversation” through a semi-structured interview, as explained in the EUnetHTA document “Patient input in Relative Effectiveness Assessments” [14]. Details can be found in Section 8.

2.8 Description of the evidence used

Table 2-1: Main characteristics of studies included

Author and year (study name)	Study type	Number of patients	Upper-Airway Stimulation device	Main endpoints	Included in clinical effectiveness and/or safety domain
Woodson 2018 (STAR) [15]	Multicenter (15 centers) prospective and retrospective observational registry	126	Inspire™	Changes of apnea-hypopnea index (AHI) Therapy usage; Changes in daytime sleepiness and patient-reported response to therapy experience. Clinical Global Impression–Improvement (CGI-I); Any event related or possibly related to the procedure and/or the therapy.	EFF/SAF
Kezirian 2014 (APNEX-UAS) [16]	Multicenter (8 centers) prospective and retrospective observational registry	31	Apnex™	Mean change in apnea-hypopnea index (AHI) and FOSQ total score. Usage endpoints: proportion of nights used and nightly hours of use. Rate of freedom from serious adverse events.	SAF
Steffen 2019 (G-PMS) [17]	Multicenter (3 centers) prospective and follow-up observational registry	60	Inspire™	Changes in apnea-hypopnea index (AHI) Therapy usage: hours per week; Oxygen Desaturation Index (ODI); Any event related or possibly related to the procedure and or the therapy.	EFF/SAF
Eastwood 2019 (BLAST OSA) [18]	Multicenter (8 centers) prospective single-arm	27	Genio™	Device-related serious adverse events; change in the apnea-hypopnea index (AHI); Oxygen Desaturation Index (ODI).	SAF
Hofauer 2019 G-PMS) [19]	Multicenter (2 centers) prospective and follow-up observational registry	102	Inspire™	Therapy usage: hours per week and self-reported adherence to UAS.	EFF
Friedman 2016 (THN) [20]	Open-label, prospective, multicenter (7 centers), single-arm cohort study	46	aura6000™ System	Serious adverse events (SAEs); Changes in apnea-hypopnea Index (AHI) and Oxygen Desaturation Index (ODI).	SAF

Author and year (study name)	Study type	Number of patients	Upper-Airway Stimulation device	Main endpoints	Included in clinical effectiveness and/or safety domain
Thaler 2019 (ADHERE) [21]	registry, international, multicenter, prospective observational	1,017	Inspire™	Changes in apnea-hypopnea index (AHI) from baseline to post-titration; Therapy usage: hours per week; Changes in daytime sleepiness and patient-reported responses to therapy; any event related or possibly related to the procedure and or the therapy; Clinical Global Impression–Improvement (CGI-I).	EFF/SAF
Woodson 2014 (STAR) [22]	multicenter, RCT(Sham-control)	46 (23/23)	Inspire™	Changes in apnea-hypopnea index (AHI) from baseline to post-titration; Therapy usage; Changes in daytime sleepiness and patient-reported responses to therapy experience; any event related or possibly related to the procedure and or the therapy; Clinical Global Impression–Improvement (CGI-I).	EFF

Abbreviations: AEs: adverse events; AHI: apnea-hypopnea index; CGI-I: clinical global impression–improvement; EFF: effectiveness; FOSQ: functional outcomes of sleep questionnaire; RCT: Randomized Control Trial; ODI: Oxygen Desaturation Index; SAF: safety; UAS: Upper airway stimulation.

2.9 Deviations from project plan

Although the project plan indicated that only comparative studies would address questions related to effectiveness, information from prospective single-arm studies was considered useful for those outcomes involving longer follow-up periods: adherence, quality of life, mortality, cardio and cerebrovascular events. Only prospective studies with data on more than 10 patients were accepted for this deviation from the project plan.

The rating of outcomes led to the removal of one outcome initially mentioned in the project plan: “Technical and Procedural Success”. The authoring team determined that there was no established definition for this outcome, which had been rated as non-critical. A detailed explanation of this issue can be found in the Discussion section (Discussion of the quality of evidence

).

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is Hypoglossal Nerve Stimulation (HGNS) in patients with moderate-to-severe obstructive sleep apnea (OSA)? What are positive airway pressure (PAP) systems? What are other non-invasive procedures used in patients with moderate-to-severe obstructive sleep apnea (OSA)?
A0020	For which indications has the HGNS received marketing authorization or CE marking?
B0002	What is the claimed benefit of HGNS in relation to the comparator(s)?
[**B0003**	What is the phase of development and implementation of HGNS and comparators?
B0004	Who administers HGNS, PAP systems or other non-invasive procedures used in OSA patients and in what context and level of care are they provided?
B0009	What equipment and supplies are needed to use HGNS and the comparators?
A0021	What is the reimbursement status of HGNS?

3.2 Results

Features of the technology and comparators

[B0001] – What is Hypoglossal Nerve Stimulation (HGNS) in patients with moderate-to-severe obstructive sleep apnea (OSA)? What are positive airway pressure (PAP) systems? What are other non-invasive procedures used in patients with moderate-to-severe obstructive sleep apnea (OSA)?

The technology under assessment is the Hypoglossal Nerve Stimulation (HGNS) for moderate-to-severe obstructive sleep apnea (OSA).

Obstructive sleep apnea causes breathing to repeatedly stop for short periods during sleep. It can develop due to a variety of physiologic and anatomical causes. The tongue may fall backwards and contribute to the narrowing of the upper airway [23,24].

One of the important pathogenic risk factors for OSA is decreasing tone of the upper airway dilator muscles (e.g., the genioglossus) during sleep [24]. Electrical stimulation of the genioglossus muscle via intramuscular or transcutaneous electrodes has been explored. Since sleep can be disrupted by sensory phenomena during transcutaneous stimulation, direct electrical stimulation of the motor nerve innervating the genioglossus muscle, the hypoglossal nerve (HGN), has been explored as an alternative option, and constitutes the intervention of interest for this HTA report [25-27].

HGNS is an innovative treatment for OSA that uses neuromodulation via an implantable stimulatory device, resembling a pacemaker, which promotes airway patency throughout the night and thus improves sleep in OSA patients. There are several HGNS models, but two manufacturers have their systems in the marketplace: the Inspire® Upper Airway Stimulation (UAS) System (Inspire Medical

Systems, Inc.) and the aura6000™ System (ImThera Medical, Inc.). Besides these, there are at least two other models that are either no longer available (HNS/HGNS® System Apnex Medical, Inc., officially ceased operations in March 2013 because of an unsuccessful clinical trial) or are investigational devices not for sale in Europe or the US [Nyxoah SAT Genio™ System (Nyxoah)].

The system consists of a nerve stimulator implant, a battery for the stimulator [either internal (Inspire®, aura6000™) or external (Genio™)] and in the case of Inspire®, a breathing pattern sensor also comes integrated. A remote control can also be included (Inspire®, aura6000™)[28].

Hypoglossal nerve stimulation involves a surgical procedure for device implantation. HGNS effect derives from enhancing the upper airway neuromuscular tone in order to reduce the collapsibility, thereby maintaining an open airway during sleep [29].

Technical description of HGNS Systems

- Inspire® Upper Airway Stimulation (UAS) therapy consists of a breathing sensor and a stimulation lead, powered by a small battery, which are both implanted. The breathing sensor is a pulmonary pressure sensor to detect respiration. The neurostimulator delivers electrical stimulating pulses to the hypoglossal nerve through the stimulation lead; the stimulating pulses are synchronized with the ventilation detected by the sensing lead. The system delivers mild stimulation to key airway muscles.

- The aura6000™ System (ImThera Medical, Inc.) consists of an implanted pulse generator (IPG), a small implant containing the battery and stimulation system, and a multi-electrode lead with a silicone cuff housing six independent electrodes connected to the IPG. The device stimulates both tongue protrusors and retractors in order to stiffen the posterior aspect of the tongue and pharyngeal walls, thanks to the more proximal location of the electrodes.

- The Nyxoah SAT Genio™ System (Nyxoah) is an ultra-small neurostimulator that measure 20mm in diameter and is 2.5mm thick. Its principal difference is that the energy battery is placed outside the body and the stimulator implant (SI) is designed to be placed in the chin area, like a “saddle on a horse” on the genioglossus muscle, in contact with both branches of the hypoglossal nerve, with the advantage of bilateral nerve stimulation.

The purpose of the remote for the Inspire® UAS and aura6000™ systems is to allow for starting and stopping of the therapy. For the aura6000™, the remote also has a charging function as the battery inside the IPG is rechargeable [7,30] .

Table 3-1: Features of the intervention and comparators

	Hypoglossal Nerve Stimulation Systems (HGNS) Technology	**Hypoglossal Nerve Stimulation Systems (HGNS) Technology**	**Hypoglossal Nerve Stimulation Systems (HGNS) Technology**
Name	Inspire® Upper Airway Stimulation (UAS) System	aura6000™ System	Nyxoah’s Genio™ System
Proprietary name	Inc. Maple Grove, Minnesota, USA	Imthera® Medical USA (a subsidiary of LivaNova plc., London, UK)	
Manufacturer	Inspire Medical Systems, Inc. Golden Valley, Minnesota, USA	ImThera Medical, Inc./LivaNova San Diego, CA, USA	Nyxoah S.A. 1435 Mont-Saint-Guibert, Belgium

	Hypoglossal Nerve Stimulation Systems (HGNS) Technology	Hypoglossal Nerve Stimulation Systems (HGNS) Technology	Hypoglossal Nerve Stimulation Systems (HGNS) Technology
Names in other countries	Inspire UAS System (USA); Inspire® Therapy	Sleep Apnea Implant Therapy; THN Sleep Therapy aura6000™ OSA System	Nyxoah Genio™ System (UK)
Reference codes	P130008	REG-00841 –01, REV AB 2807429CN (Version 11)	
Class/GMDN code	PMA for Inspire UAS system, which includes the Model 3024 Implantable Pulse Generator, the Model 4063 Stimulation Lead, the Model 4323 Sensing Lead, the Model 2740 Physician Programmer and the Model 3032 Patient Programmer.		
Technical characteristics			
Implanted pulse generator (neurostimulator)	Right ipsilateral mid-infraclavicular region	Upper chest rechargeable battery; recharging performed transcutaneously with external remote control charger	An investigational device, not for sale in Europe or the US.
Stimulation lead	Synchronized with ventilation cuff section with 3 electrodes. The polarity of the electrodes has to be determined. There is only one anode and one cathode.	Multi-electrode lead: 6 independent electrodes. All 6 electrodes are cathodes, the anode being part of the implant.	
Respiration sensing lead	Sensing side facing the pleura pulmonary pressure sensor		

Abbreviations: UAS = Upper-Airway Stimulation;

Sources: user manuals/technical documents [31]

Under general anaesthesia, with both the Inspire® and aura6000™ systems, a neurostimulator is implanted in the chest and a stimulating lead is placed on the main trunk of the hypoglossal nerve. The role of the neurostimulator is to deliver electrical pulses to the hypoglossal nerve. For Inspire®, the sensing lead measures changes in breathing. The respiratory-sensing leads are positioned between the external and internal intercostal muscle. The stimulator is programmed and controlled wirelessly to adapt to specific patient needs [23].

In conclusion, Hypoglossal Nerve Stimulation (HGNS) has emerged as an alternative approach, based on upper-airway stimulation [31], for moderate-to-severe OSA patients who fail CPAP. It is a medical procedure in which a device consisting of different units capable of stimulating the hypoglossal nerve to control upper-airway collapsibility are implanted in different locations according to each manufacturer's protocol. The aim is to keep the airway open during sleep [23]. The hypoglossal nerve stimulator (HGNS) is currently approved for the treatment of obstructive sleep apnea (OSA) in patients with a definite prerequisite for CPAP intolerance. A complete sleep medicine assessment, as well as an evaluation of patient history, systemic disorders, craniofacial and upper airway anatomy, and other confounding factors should be performed [32,33].

What are positive airway pressure (PAP) systems?

The conservative treatment for OSA is represented by continuous positive airway pressure (CPAP) or mandibular repositioning devices [5].

Continuous Positive Airway Pressure (CPAP) is the most common treatment for OSA (and is considered the gold standard therapy), even if patients perceive the device as difficult, noisy, and/or

annoying to use and disruptive to sleep. CPAP treatment requires patients to wear a mask or nasal prongs over the nose (or nose and mouth) during sleep. The mask is connected to a small air pump. CPAP increases the pressure in the oropharyngeal airway, thereby maintaining an open airway. This approach must be used each night to be effective. The procedure is uncomfortable and disruptive for patients, especially during the early stages of treatment.

The CPAP machine delivers a positive stream of air pressure that acts as a pneumatic splint to maintain the opening of the airway during sleep. The intervention requires patients to wear a nasal or full-face mask while sleeping. Compliance in the home setting is often poor, with only 40 to 60% of patients using the treatment long-term or as prescribed. When adherence is defined as greater than 4 hours of nightly use, 46 to 83% of patients with obstructive sleep apnea have been reported to be non-adherent to treatment [34–36].

In children, CPAP is indicated when all of the following criteria are met: OSA diagnosis has been established by PSG (polysomnography); an adenotonsillectomy has been unsuccessful or is determined to be clinically inappropriate, or when definitive surgery is indicated but must await complete dental and facial development [37].

CPAP improves hypoxemia and respiratory parameters, such as the apnea-hypopnea index (AHI) or the oxygen desaturation index (ODI). The success of positive airway pressure (PAP) is significantly limited by patient non-compliance due to noise, discomfort, mask fit, claustrophobia, allergies or nasal and sinus structures [38].

According to the American Academy of Sleep Medicine (AASM) [39], four recommendations are strongly suggested for PAP treatment of OSA in adults and include:

- using PAP to treat excessive sleepiness
- initiating PAP therapy with either APAP at home or an in-laboratory CPAP titration
- continuing PAP therapy for OSA with either CPAP or APAP
- using educational interventions to initiate PAP therapy in adults with OSA

PAP failure is defined as an inability to eliminate OSA (AHI of greater than 20 despite PAP usage), and PAP intolerance is defined as: (1) Inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night), or (2) Unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it) [40].

What are other non-invasive procedures used in patients with moderate-to-severe obstructive sleep apnea (OSA)?

Although positive airway pressure (PAP) is the gold-standard for treatment, long-term compliance with this modality is low [27]. Various alternatives to PAP therapy, including oral appliance therapy, upper-airway surgery, orthognathic surgery, and hypoglossal nerve stimulation (HGNS) have been developed and implemented. Novel treatments inducing substantial reduction of OSA and improving associated daytime symptoms have made it possible to treat patients who do not respond to PAP [28] .

Other treatment options for CPAP in OSA include improving CPAP tolerability, increasing CPAP adherence through patient interventions, weight loss/exercise, positional therapy, nasal expiratory positive airway pressure, oral pressure therapy, oral appliances, surgery, hypoglossal nerve stimulation, drug treatment, and combining two or more of the aforementioned treatments. Despite the many options available to treat OSA, none are as efficacious as CPAP. The benefits of these alternatives are higher tolerability and adherence rates than those using CPAP, making them a more viable treatment option for long-term use [3].

The main reasons for conservative therapy failure include non-acceptance, side effects and/or inefficacy. Approximately one-third of patients experience such difficulty with chronic CPAP use that they seek other options or choose to remain untreated [28]. With OSA surgery there are procedures regarded as minimally invasive such as radiofrequency or palatal stiffening. These procedures are performed in mild OSA as they are minimally effective. Conventional surgery includes palatopharyngeal surgery (classical UPPP and the new pharyngoplasties that have been more commonly performed in recent years worldwide) or tongue-based surgery. Laser-assisted uvuloplasty (LAUP) is not recommended. Likewise, for OSA patients who have failed conservative treatments, hypoglossal nerve stimulation (HGNS) may be indicated [5,41].

As classical UPPP is not currently the preferred technique, new pharyngoplasties are being used, in which tissue removal is not paramount. Muscle remodelling is being performed such that the pharynx is less collapsible and results in fewer side effects [42].

While UPPP has enjoyed only modest success in unselected patients, in selected patients a cure rate of over 80% can be achieved [43]. For example, OSA is characterized by reduced stimulus to the upper-airway muscles. In fact, upper-airway patency has been strongly correlated with activation of the genioglossus muscle. Therefore, upper airway stimulation has been explored as a physiologic alternative to the anatomic approach of UPPP.

Patients who fail UPPP may be candidates for positional therapy, MAD, HGNS or additional procedures such as hyoid suspension, maxillary and mandibular osteotomies, or modification of the tongue [5].

[B0002] – What is the claimed benefit of the HGNS in relation to the comparator(s)?

The principal expected benefit of this technology is a significant reduction in obstructive sleep apnea, as well as improvements in the quality of sleep and quality of life in OSA patients who do not accept or tolerate CPAP. The benefits to overall health, cardiovascular morbidity and mortality needs to be scientifically confirmed in the long-term [29].

According to an ECRI brief release on the Inspire Upper Airway Stimulation System, the available evidence suggests that use of this technology is relatively safe and at least as effective as surgery for reducing nocturnal apnea and improving sleep and quality of life (QOL) in patients with OSA who cannot tolerate or who have failed CPAP or BiPAP therapy. In any case, further validation studies are needed to address evidence gaps [40].

The majority of studies and assessment reports on HGNS have presented short-term data. A German post-market study that followed approximately 60 patients from three implanting centers for several years concluded that respiratory and sleepiness efficacy outcomes were sustained over 2 and 3 years. Nevertheless, more long-term follow-up studies are needed [32].

[B0003] – What is the phase of development and implementation of HGNS and the comparator(s)?

HGNS systems have been increasingly implemented during the last 10 years.

The Inspire® Upper Airway Stimulation (UAS) system was the first HGNS device commercially available and CE Marked in Europe (in 2010), followed by the LivaNova / ImThera Medical's aura6000™ device, which gained a CE Mark in March 2012 and eventually received FDA investigational device exemption (IDE) for THN2 and THN3 trials. Finally, Nyxoah's Genio™ system, which gained a CE Mark in March 2019, albeit under FDA regulations, in fact, Nyxoah's Genio™ system gained an IDE for the clinical study NCT02312479 (see Table A13 in Appendix 2).

Since 2012, these systems received the generic name of Hypoglossal Nerve Stimulation (HGNS), indicating their use for targeting upper-airway stimulation. In OSA, these devices are chosen for patients who fail PAP therapy.

Over the last ten years, HGNS systems have been approved and developed in two or three cycles such that the models implemented and currently available on the health market represent updated versions (see Table A13 in Appendix 2) with significant technical improvements that bring added value in terms of effectiveness and safety for patients.

[B0004] – Who administers HGNS, PAP systems or other non-invasive procedures used in OSA patients and in what context and level of care are they provided?

HGNS is administered after a thorough patient examination that may include a drug-induced sleep endoscopy (this is the case for Inspire® and Genio™, but not for Aura6000®) and an in-laboratory diagnostic polysomnographic examination [29]. The device is implanted by a surgeon experienced in cranial nerve anatomy and surgical techniques (AT Implant manual), under general anaesthesia, usually in a hospital setting, and most patients are discharged within 3-4 days after the procedure, returning to the sleep-lab 1 month later where the system is activated and adjusted by a physician trained in sleep medicine. Patients are instructed how to use the device and are scheduled for regular follow-up visits. All medical teams need to undertake specific training before using the device [31].

Surgical methods used to correct obstructions in OSA patients are uvulopalatopharyngoplasty (UPPP), tonsillectomy and nasal surgery. Tonsillectomy and nasal surgery are commonly performed in otolaryngology practice. Isolated nasal surgery in OSA patients with nasal obstructions reduces the therapeutic CPAP device pressure required [27,40,44,45].

The most common treatment for OSA is CPAP treatment, which requires patients to wear a mask or nasal prongs while sleeping. Compliance in the home setting is often poor, with only 40-60% of patients using the treatment long-term or as prescribed [27,40,44].

There is a variety of oral appliances to treat patients with OSA (including clasps, restricted elastic bands, or pressure tubes to open the airway). These are less commonly used due to the greater potential for patient discomfort [40].

[B0009] – What equipment and supplies are needed to use HGNS and the comparators?

The procedure is usually performed in an inpatient setting. For implanting the neurostimulator and the lead, a sterile surgical theatre is needed. The implanting procedures require a specialised oto-rhinolaryngologist with a supporting team, as well as a physicist and equipment for neuromonitoring. Several instruments are needed to carry out this minimally invasive procedure (a knife for incisions, a subcutaneous tunnelling device, etc.). A sleep laboratory and specialists in sleep medicine are also required. An endoscopy unit may be necessary (this is not the case for the aura6000™) [29].

Although the concept behind stimulation is now commonplace, each device has distinct activation strategies that are reflected in the different components of each product (see Box 1).

Box 1. The components of the HGNS systems

The **Inspire system** has three implantable components: - a *stimulation lead* that delivers mild stimulation to maintain multilevel airway patency during sleep, - a *breathing sensor lead* that detects breathing patterns, - a *generator* that monitors breathing patterns. The two *external components* are: - a *patient sleep remote* that provides a non-invasive means for the patient to activate the generator and - a *physician programmer* that allows the physician to noninvasively query and configure the generator settings. The system battery life for the implantable components is 7 to 10 years	The **aura6000™ IPG and lead** are part of the THN Sleep Therapy® System used for the treatment of obstructive sleep apnea (OSA). It consists of an implanted pulse generator (IPG), a small implant containing the battery and stimulation system (hardware and software), and a multi-electrode housing six independent electrodes, connected to the IPG via a subcutaneously tunnelled lead wire. The IPG battery is rechargeable. Recharging is performed transcutaneously with an external remote-control charger (RCC) and charging coil that is placed over the IPG with the help of two magnets. The same RCC is used to start, pause and end each night session of stimulation. The IPG has a log memory to record actual charging and use. The system battery life is of 12 to 15 years. Other components include: - the *handheld remote control* and *charger* (RCC or remote; model 500.0100), - charging *antenna* (antenna; model 500.0300), and - *aura6000 clinical manager* (aCM; model 700.0100) software. [R18 /ART].	The **Nyxoah Genio™ System** consists of three components: - an *implantable stimulation device,* - an *activation chip* and *disposable patch,* and - a *charging unit*. The tiny neurostimulator is implanted under the chin using *a minimally invasive procedure***.** The stimulator's electrodes are placed in contact with both branches of the hypoglossal nerve.

[A0020] – For which indications has the HGNS received marketing authorization or CE marking?

Inspire® Upper Airway Stimulation (UAS) therapy received a CE Mark approval in 2010 for treating a subset of patients with moderate-to-severe OSA [29,31].

In April 2014, the Inspire® system received FDA approval through the premarket approval (PMA) process as a second-line therapy option for a subset of patients with symptomatic moderate-to-severe OSA: AHI ≥20 and ≤55 in adult patients aged 22 years and older who have been confirmed to fail or who cannot tolerate Positive Airway Pressure (PAP) treatments, and who do not present complete concentric collapse at the soft palate level. A Supplemental PMA approval was granted in June 2017 that expanded the approved lower limit of the AHI range from 20 to 15 [29,31].

As highlighted in the CE Marked System Implant Manual, Inspire Upper Airway Stimulation therapy is intended to treat moderate-to-severe OSA (15 ≤ AHI ≤ 65) by improving airway patency through stimulation of the hypoglossal nerve, synchronized with respiration, to elicit a neuromuscular response at the base of the tongue. In addition to patients with complete concentric collapse of the soft palate or any anatomical finding (e.g., malformations for surgical resections), contraindications for the use of Inspire Upper Airway Stimulation therapy include: patients who have severely compromised neurological control of the upper airway, women who are pregnant or plan to become pregnant, patients with a previous surgery on the soft-palate tissue within 3 months, those whose tissue is hypersensitive to being in contact with foreign material or those who require magnetic resonance imaging (MRI) other than what is specified in the MR Conditional labelling [31].

Inspire is the only UAS system available in the United States [40] for treating Obstructive Sleep Apnea [32].

Apnex Medical, Inc. received a CE Mark approval for its HNS/HGNS® System in 2011 for patients suffering from obstructive sleep apnea. The system was approved for sale in Europe. Apnex Medical, Inc. received investigational device exemption (IDE) approval from the U.S. FDA to conduct a clinical study. Apnex Medical, Inc. officially ceased operations in March 2013 because of an unsuccessful clinical trial [29].

The LivaNova / ImThera Medical's aura6000™ device received a CE Mark in 2012 for the treatment of OSA [29,31] and is available for sale in Germany, Austria, Spain, Portugal, Israel & Colombia under the CE label. In 2014, the FDA approved an investigational device exemption (IDE) for the aura6000™ System for the clinical study NCT02263859 (THN3). The device is still under trial in the USA. [29].

Nyxoah's Genio™ system gained a CE Mark in March 2019 and the manufacturer is now seeking FDA approval [31,46].

[A0021] – What is the reimbursement status of HGNS?

The results of a survey among EUnetHTA WP4 OT partners, answered by 10 partners from 8 countries, showed that HGNS is reimbursed only in Germany for use in the hospital sector, and in the UK if used in conformance with specific guidelines (Table A14).

The Inspire dossier also references several guidelines and includes published positive-support statements related to HGNS therapy in selected patients, such as the following: recommendation by the German Society for Sleep Research and Sleep Medicine (DGSM) and the Dutch Guidelines for the Treatment of Obstructive Sleep Apnea.

While the 2018 Blue Cross Blue Shield Association's Evidence Street HTA report stated that "The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome for patients meeting the selection criteria which are based on information from clinical study populations and clinical expert opinion", the 2018 ECRI Institute Health Technology Assessment – Product Brief concluded that "Controlled studies with larger patient populations are needed to confirm the findings" [40].

The Australian Health Policy Advisory Committee on Technology (HealthPACT) published a brief on Upper Airway Stimulation for Moderate-to-Severe Sleep Apnea in March 2015 which concluded that "it is unlikely this device will diffuse into the jurisdictions within the next one to three years", and "should the therapy be introduced, HealthPACT recommended that the technology be monitored for 24 months" [44].

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is moderate-to-severe obstructive sleep apnea (OSA) in the scope of this assessment?
A0003	What are the known risk factors for OSA?
A0004	What is the natural course of OSA?
A0005	What are the symptoms and the burden of OSA?
A0024	How is OSA currently diagnosed according to published guidelines and in practice?
A0025	How is OSA currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is HGNS utilized?

4.2 Results

Overview of the disease or health condition

[A0002] – What is moderate-to-severe obstructive sleep apnea (OSA) in the scope of this assessment?

Obstructive sleep apnea (OSA) is a potentially serious sleep disorder in which breathing repeatedly stops and starts during sleep. It results from an upper airway collapse during sleep due to inadequate motor tone of the tongue and/or airway dilator muscles. It has been associated with intermittent hypoxia and transient arousals. Collapsibility can also be increased by underlying anatomic problems. Obesity and, particularly central adiposity, are both potent risk factors for sleep apnea. Indeed, these two factors can heighten the risk of pharyngeal collapse due to the mechanical effects they exert on pharyngeal soft tissues [47].

OSA, which is characterized by repetitive ≥ 10-second interruptions (apnea) or reductions (hypopnea) in airflow, can be initiated by partial or complete collapse of the upper airway despite respiratory efforts [40].

The apnea-hypopnea index (AHI) is commonly used to categorize the severity of OSA and represents the average number of apneas and/or hypopneas per hour of recorded sleep [29]. In adults, an AHI of less than 5 events per hour is considered normal. Mild OSA is defined as an AHI between 5 and 15 events per hour, moderate OSA between 15 and 30 events per hour, and severe OSA as greater than 30 events per hour [48] – see Table 4-1.

Table 4-1: Grades of severity in OSA

OSA grade of severity	In adults	In children
Mild OSA	AHI of 5 to <15	AHI ≥ 1.5 is abnormal
Moderate OSA	AHI of 15 to <30	
Severe OSA	AHI ≥ 30	AHI of ≥ 15

Abbreviations: AHI = Apnea-Hypoxia Index (normal AHI < 5); OSA: Obstructive Sleep Apnea

Source: [5,49]. These criteria may differ by country (in Spain, OSA in children is regarded as severe when the AHI >10).

An apnea is defined as the complete cessation of airflow for at least 10 seconds. Apneas are further classified as obstructive, central, or mixed, based on whether the effort to breathe is present during the event. A hypopnea is defined as a reduction in airflow that is followed by an arousal from sleep or a decrease in oxyhemoglobin saturation. Commonly used definitions of a hypopnea require a 25% or 50% reduction in oronasal airflow associated either with a reduction in oxyhemoglobin saturation or an arousal from sleep [29,50,51]. Central sleep apnea (CSA) describes a group of conditions in which cessations in air flow occur without respiratory effort. In contrast, obstructive sleep apnea patients have ongoing respiratory effort during respiratory events. However, considerable overlap exists in the pathogenesis and clinical presentation of obstructive sleep apnea and CSA [43]. Mixed apneas are characterized by absent respiratory effort and airflow in the initial part of the event and respiratory effort without airflow in the last part. The pathophysiology is based on coexisting ventilatory control instability and upper airway collapsibility[52]. To further differentiate between central and mixed patterns, some studies excluded patients with a central and/or mixed respiratory event index (REI: number of apneas + hypopneas per hour) >25% of the AHI [7,22,53]. Patients diagnosed with central sleep apnea syndrome are not relevant to this report.

[A0003] – What are the known risk factors for OSA?

Several factors can increase the risk of developing OSA. These include: obesity, male gender, heritable factors, craniofacial and upper airway abnormalities, alcohol consumption prior to sleep and night-time nasal congestion. Age is also a risk factor, with a higher prevalence between 40-70 years of age [29,44]. The best documented risk factor for OSA is obesity [29,54].

[A0004] – What is the natural course of OSA?

OSA patients can develop multiple complications due to intermittent hypoxia, sympathetic nervous system activation, and alterations in intrathoracic pressures. The cardiorespiratory changes result in an increased risk of arterial hypertension, coronary artery disease, and stroke. The most severely affected patients may develop respiratory failure and subsequent heart failure. OSA is associated with metabolic abnormalities, such as type 2 diabetes and significantly increases the risk of insulin resistance and sudden death [29,31,54].

It also impacts quality of life outcomes such as daytime functioning and daytime sleepiness, cognitive dysfunction, impaired work performance, and decrements in health-related quality of life, as well as increasing the risk of traffic accidents [28,29].

Effects of the disease or health condition

[A0005] – What are the symptoms and burden of OSA?

OSA is suspected when snoring, witnessed apneas and daytime sleepiness appear and deteriorate the patient's quality of life and sleep. Clinical symptoms include unintentional sleep episodes during

wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, insomnia, snoring and cognitive impairment [55]. According to the American College of Physicians, disrupted sleep can result in hypersomnolence and impaired concentration during the day, increased probability of motor vehicle and other accidents, and decreased quality of life. Although evidence establishing a causal relationship is not currently available, OSA is associated with adverse clinical outcomes, including: cardiovascular disease, hypertension, cognitive impairment and metabolic abnormalities, such as type 2 diabetes; and an increased risk for postoperative cardiac and respiratory complications [54].

OSA has an important impact on QOL. CPAP effectively normalizes sleep parameters in patients with OSA [33]. The sleep apnea quality of life index (SAQLI) is a specific indicator measuring the impact of OSA on QOL and in prospective case series examining HGNS therapy, there was a statistically significant improvement in the mean SAQLI at 6-months of follow-up [20]. In addition, the Functional Outcomes of Sleep Questionnaire is a disease-specific quality-of-life measure that assesses the impact of excessive sleepiness disorders on functional outcomes relevant to daily behaviours and quality of life. The results of prospective studies, including data on the FOSQ, showed significant improvement, which was independent of the follow-up length [7,53].

The burden of undiagnosed and untreated OSA on the healthcare system is significant, with increased healthcare utilization seen in those with untreated OSA, highlighting the importance of early and accurate diagnosis of this common disorder. Treatment of OSA has been shown to improve QOL, lower the rates of motor vehicle accidents, and reduce the risk of the chronic health consequences of untreated OSA. There are also data supporting a decrease in healthcare utilization and cost following the diagnosis and treatment of OSA [56].

In addition, the level of AHI is a predictor for some clinical outcomes [54]:

Outcome	Evidence	Overall Quality of Evidence
All-cause mortality	Association with increased risk with AHI score >30 events/h	High
Cardiovascular mortality	Inconsistent results	Insufficient
Nonfatal cardiovascular disease	Association with increased risk with AHI score ≥30 events/h and no CPAP treatment	Insufficient
Stroke	No association	Insufficient
Hypertension	Unclear conclusions	Insufficient
Type 2 diabetes	Association with increased risk with AHI score >30 events/h	Low
Quality of life	No association	Insufficient

AHI: apnea–hypopnea index; CPAP: continuous positive airway pressure.

OSA affects millions of people worldwide, and its prevalence is increasing with the greater incidence of obesity and an ageing population [57].

In terms of cost infrastructure and economic consequences, little evidence has been published to date, though an Australian study found significant economic impact on the nation's healthcare system. In fact, a cost analysis performed in 2010 estimated that sleep disorders cost the Australian hospital system $96.2 million, of which 59.6% was attributed to OSA. The out-of-hospital cost of OSA was estimated to be $96.6 million and the cost to the healthcare system for conditions attributed to OSA (cardiovascular disease, depression and anxiety, motor-vehicle and workplace injuries) was an estimated $408.5 million in 2010 [58]. In addition, the total average cost per DRG (E63Z sleep apnea) was equal to $1,612 [44].

Current clinical management of the disease or health condition

[A0024] – How is OSA currently diagnosed according to published guidelines and in practice?

Polysomnography performed in a sleep laboratory has been the standard method to diagnose OSA [29,57]. Diagnosis and severity of OSA is based on polysomnography. A patient suspected of OSA must undergo an overnight sleep study that monitors cardiorespiratory and electroencephalographic variables, and documents periodic movements in sleep, such as activity of the legs [59].

The American College of Physicians recommended the following in 2014: (1) a sleep study for patients with unexplained daytime sleepiness; (2) polysomnography for diagnostic testing in patients suspected of obstructive sleep apnea; (3) portable sleep monitors in patients without serious comorbidities as an alternative to polysomnography when the latter is not available for diagnostic testing [60].

In 2017, Kapur et al. [56] published a set of recommendations based on an American Academy of Sleep Medicine commissioned study, as a guide for clinicians diagnosing OSA in adults. These are:

1. We recommend that clinical tools, questionnaires and prediction algorithms not be used to diagnose OSA in adults, in the absence of polysomnography or home sleep apnea testing. (STRONG).
2. We recommend that polysomnography, or home sleep apnea testing with a technically adequate device, be used for the diagnosis of OSA in uncomplicated adult patients presenting signs and symptoms that indicate an increased risk of moderate-to-severe OSA. (STRONG).
3. We recommend that if a single home sleep apnea test is negative, inconclusive, or technically inadequate, polysomnography be performed for the diagnosis of OSA. (STRONG).
4. We recommend that polysomnography, rather than home sleep apnea testing, be used for the diagnosis of OSA in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia. (STRONG).
5. We suggest that, if clinically appropriate, a split-night diagnostic protocol, rather than a full-night diagnostic protocol for polysomnography be used for the diagnosis of OSA. (WEAK).
6. We suggest that when the initial polysomnogram is negative and clinical suspicion for OSA remains, a second polysomnogram be considered for the diagnosis of OSA. (WEAK).

According to ICSD-3 (International Classification of Sleep Disorders – Third Edition), an obstructive apnea is diagnosed when the breathing disorder cannot be explained by any other sleep disorder or medical condition, or by the use of drugs or other substances, and an apnea–hypopnea index (AHI) >15/h (each event ≥10 s) sleep time or an AHI ≥5/h sleep time in combination with a typical clinical pathology or relevant comorbidity is present [65].

Daytime sleepiness up to the extent of involuntarily falling asleep is the main clinical symptom of OSA. However, some affected patients exhibit no sleepiness, do not consider it to be a symptom of disease or do not explicitly notice it. Daytime sleepiness reduces productivity and, during the course of disease, also impairs cognitive ability, social compatibility, and quality of life. Sleeping partners report breathing arrests. The most important diagnostic parameter is the AHI, which reports the number of apneas and hypopneas per hour of sleep. The AHI objectifies the diagnosis and, together

with the clinical symptoms and comorbidities, determines the severity of OSA. An AHI >15/h and <30/h is defined as moderate, and an AHI >30/h as severe OSA [65].

The diagnostic instruments are oriented to the pathophysiology, consequences, and comorbidities of sleep-related breathing disorders. They serve to define the severity of the disorder and a patient's comorbidities, and should be able to estimate the extent of the consequences. They include a recording of the case history, self-rating questionnaires, in- and outpatient multichannel devices, video recording, and clinical laboratory diagnostic tests, as well as instrument-based and non-instrument-based performance tests. Depending on the particular case scenario, the diagnostic methods may be applied in combination, simultaneously or sequentially, complementarily or exclusionarily, with different demands in terms of time, personnel, organisation, and materials. The most important diagnostic instrument and the gold standard reference for sleep medicine diagnostics is supervised cardiorespiratory polysomnography (PSG) in a sleep laboratory. Recording and evaluation of the PSG should be performed according to AASM criteria (version 2.3).

Further tools used to diagnosis sleep-related breathing disorders are questionnaires like the Epworth Sleepiness Scale (ESS), Berlin Questionnaire (Berlin Q), STOP-BANG (Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference and Gender), the waist-to-height psychomotor vigilance test (PVT), Oxford Sleep Resistance Test (OSLER-test), Divided Attention Steering Simulation (DASS), Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT). These validated instruments assess complaints, impairments to well-being, symptoms, and various behavioural patterns [63].

[A0025] – How is OSA currently managed according to published guidelines and in practice?

Obstructive sleep apnea should be diagnosed and treated promptly. Board-certified sleep specialists evaluate polysomnography (PSG) results and make treatment recommendations for OSA patients. Home respiratory polygraphy with a type 3 sleep study is also used to diagnose OSA. Treatment depends in part on the severity of the sleep-disordered breathing (SDB). People with mild apnea have a wider array of options, while people with moderate-to-severe apnea should be treated with nasal continuous positive airway pressure (CPAP).

Treatment guidance

The goal of OSA treatment is to alleviate airway obstruction by reducing the number of episodes of apnea and hypopnea experienced during sleep.

Initial management consists of lifestyle advice and support to lose excess weight, stop smoking, limit alcohol consumption and avoid the use of sedatives.

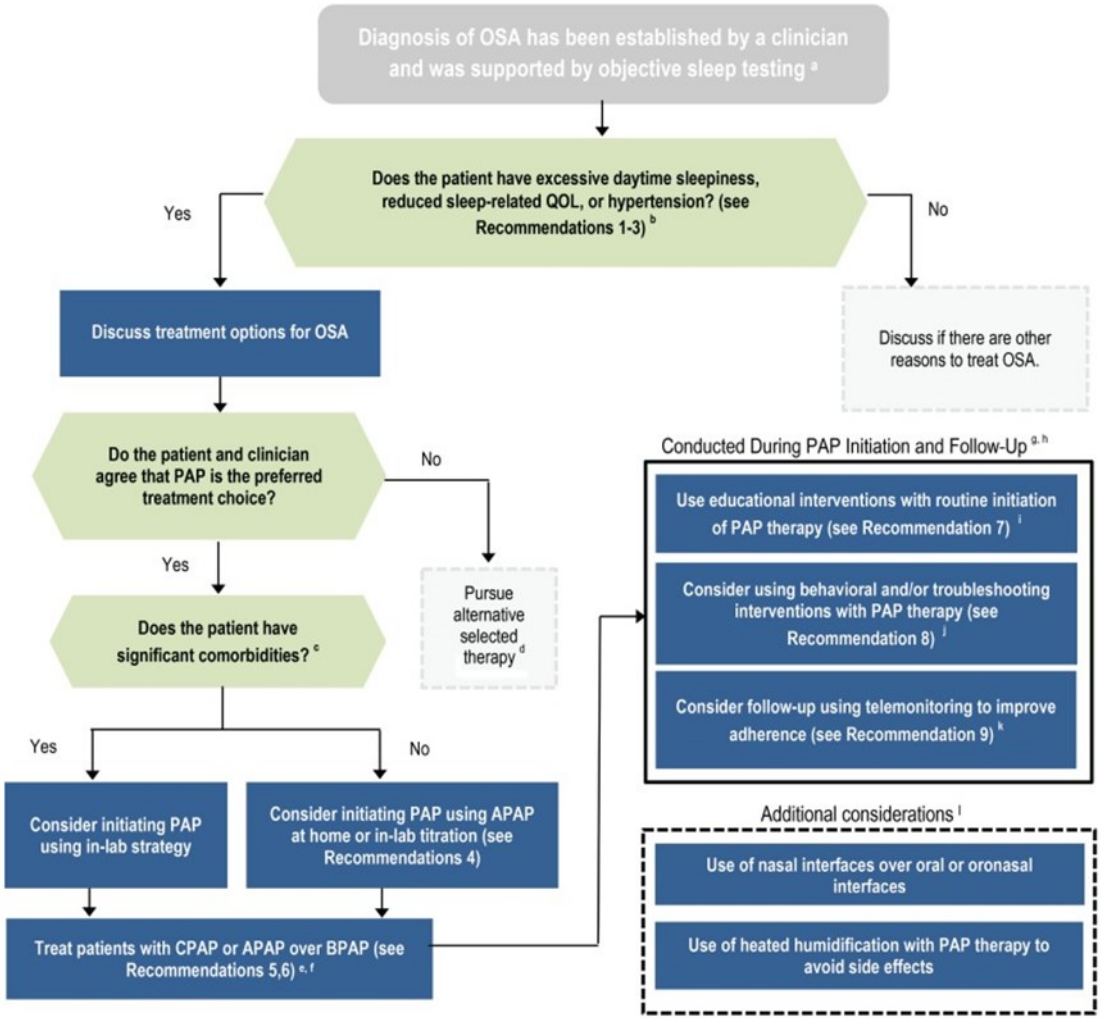
For adults with moderate or severe symptomatic OSA, the standard first-line OSA treatment involves continuous positive airway pressure (CPAP) devices whose mechanism consists of delivering compressed air into the airway to keep it open. When only CPAP therapy is considered, a certain portion of the sleep apnea population remains inadequately treated [8]. Thus, hypoglossal nerve stimulation (HGNS) has emerged as an approach for upper-airway stimulation. Alternative treatment options may include mandibular advancement devices and surgery to open up the airway.

CPAP is currently the universally accepted standard treatment for moderate-to-severe OSA. CPAP must only be initiated following a complete clinical and testing-based diagnosis performed by a

specialist. Results from the sleep study are used to determine the type of sleep apnea, the severity of the breathing disorder, and the most appropriate form of treatment. Depending on these factors, a variety of PAP devices and locations of titration of the therapy can be considered.

According to the American Academy of Sleep Medicine, the steps to follow in the CPAP therapeutic protocol are presented in the following figure.

Figure 2. Flow chart for implementation of clinical practice guideline.



a = [40]. *b = symptoms that can impair sleep-related QOL; these include, but are not limited to, snoring, sleep-related choking, insomnia, disruption of bedpartner's sleep, morning headaches, nocturia, impairments in productivity or social functioning, and daytime fatigue. c = comorbidities that may include: congestive heart failure, chronic opiate use, significant lung disease such as chronic obstructive pulmonary disease, neuromuscular disease, history of uvulopalatopharyngoplasty, those with known sleep-related oxygen requirements or expected to have nocturnal arterial oxyhemoglobin desaturation due to conditions other than OSA, including hypoventilation syndromes and central sleep apnea syndromes. d = alternative therapies that may include, but are not limited to, weight loss, positional therapy, oral appliance therapy or surgical interventions. e = BPAP is defined as a respiratory assist device that delivers inspiratory and expiratory positive airway pressure. f = BPAP devices that may need to be used for patients with therapeutic pressure requirements greater than can be provided with CPAP or APAP; the decision to use BPAP should be based on the clinician's clinical judgement and the needs of the individual patient. g = PAP therapy should be performed in conjunction with adequate follow-up to ensure proper treatment and adherence. h = recommendations included within these boxes should be considered concurrently. i = educational interventions include those focused primarily on providing information about what OSA is, downstream consequences of untreated OSA, what PAP therapy is, how to use it, and the potential benefits of PAP therapy. j = behavioural interventions include those focused on behaviour changes related to use of PAP therapy using strategies such as cognitive behavioural therapy or motivational enhancement. Troubleshooting interventions include those focused on close patient communication to identify PAP-related problems and to initiate potential solutions. k = telemonitoring interventions include those that remotely monitor data obtained from a PAP device to identify PAP-related problems and to initiate potential solutions. l = when*

implementing the above recommendations, providers should consider additional strategies that will maximize the individual patient's comfort and adherence. APAP = auto-adjusting positive airway pressure, BPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, PAP = positive airway pressure, QOL = quality of life. Source:[39]

In Europe, the services provided for the investigation and management of OSA vary from country to country. Management of OSA in different European countries is similar except for reimbursement rules, qualification of sleep specialists and procedures for titration of the CPAP treatment. The next algorithm is taken from the German Society for Sleep Research and Sleep Medicine [65].

Figure 3. Flow chart for algorithm of treatment of patients with OSA

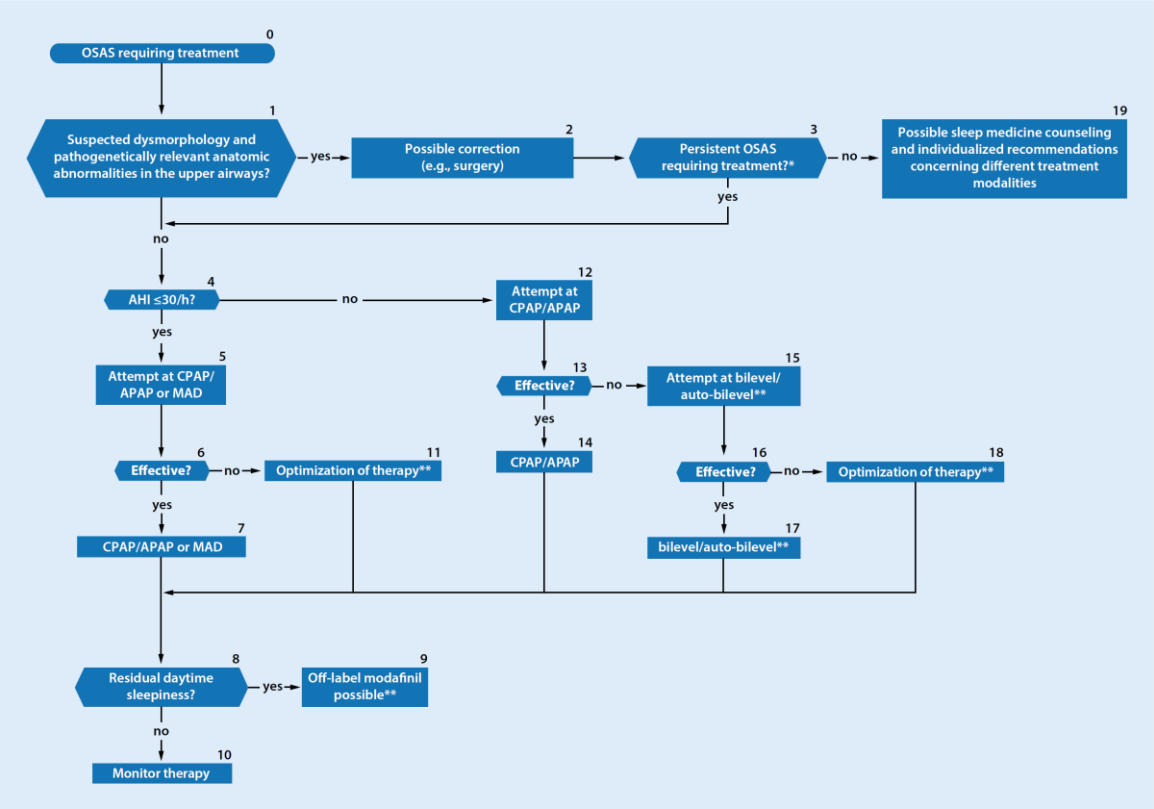


Fig. 3 ▲ Algorithm for treatment of patients with obstructive sleep apnea. *Patient training, behavioral recommendations, sleep medicine counselling; in overweight patients, weight reduction should be attempted in parallel. **In patients with an apnea–hypopnea index (*AHI*) ≤30/h and lifelong obstructive sleep apnea (*OSA*), positional therapy can be considered if no other therapy is possible or tolerated. Mandibular advancement devices (*MAD*) can also be considered in patients with severe sleep apnea who do not tolerate or refuse continuous positive airway pressure (*CPAP*), or in whom CPAP therapy cannot be used despite utilisation of all support measures. Where positive airway pressure therapies or MAD fail, in the absence of anatomic abnormalities and the presence of an AHI of 15–50/h, neurostimulation of the hypoglossal nerve (NSHG) can be used up to class I obesity, provided there is no concentric obstruction of the airways. (*OSAS* obstructive sleep apnea syndrome, *APAP* automatic CPAP)

According to the Evicore Clinical Guidelines on Sleep Apnea and Treatment, a variety of PAP device could be applied for the various forms of sleep apnea. Positive airway pressure (PAP) is produced by a flow generator and applied to the airway through nasal, oral, or oronasal mask interfaces:

- Continuous airway pressure (CPAP/APAP) device.
- Respiratory assist device, bi-level pressure (BiPAP) capability, WITHOUT backup rate feature; used with non-invasive interface - e.g., nasal or facial mask (intermittent assist device with continuous positive airway pressure device).

- Respiratory assist device, bi-level pressure (BiPAP) capability (including Adaptive Servo Ventilation (ASV), WITH backup rate feature; used with non-invasive interface - e.g., nasal or facial mask (intermittent assist device with continuous positive airway pressure device).
- Respiratory assist device, bi-level pressure (BiPAP) capability, WITH backup rate feature; used with invasive interface - e.g. tracheostomy tube (intermittent assist device with continuous positive airway pressure device).
- Humidifier, non-heated; used with positive airway pressure (CPAP/BiPAP/APAP) device.
- Humidifier, heated; used with positive airway pressure (CPAP/BiPAP/APAP) device.
- Tubing with heating element.
- Combination oral/nasal mask.
- Replacement oral cushion combo mask.
- Replacement nasal pillow comb mask.
- CPAP full face mask.
- Replacement face mask interface.
- Replacement nasal cushion.
- Replacement nasal pillows.
- Nasal interface (mask or cannula type) used with PAP device.
- Positive airway pressure headgear.
- Positive airway pressure chinstrap.
- Positive airway pressure tubing.
- Positive airway pressure filter.
- Filter, non-disposable w/ PAP.
- PAP oral interface.
- Replace exhalation port.
- Replacement, water chamber, PAP device.
- Monitoring feature/device, stand-alone or integrated, any type, includes all accessories, components and electronics, not otherwise classified (this code relates to compliance and the data download relating to a patient's PAP therapy).
- CPAP initiation and management (used to report initiation and instruction when a patient begins therapy).

Current Practice Recommendations for PAP alternatives:

- CPAP: Standard.
- BiPAP (including ST): Option if CPAP ineffective.
- ASV: a). OPTION if EF (ejection fraction) > 45% or mild central sleep apnea syndrome; b) standard against if EF ≤ 45% with moderate/severe central sleep apnea syndrome [37].

Surgical treatment

Although positive airway pressure is the first-line therapy for obstructive sleep apnea, a percentage of patients remain unable to achieve adherence to positive airway pressure [4]. Surgical treatment options aim to reduce nasal, oropharyngeal, and hypopharyngeal obstruction by different invasive procedure such as those detailed below.

a. Upper-airway surgeries

- Uvulectomy, excision of uvula.
- Palatopharyngoplasty (e.g., uvulopalatopharyngoplasty, uvulopharyngoplasty).
- Reconstruction of mandibular rami, horizontal, vertical, C, or L osteotomy; without bone graft.
- Reconstruction of mandibular rami, horizontal, vertical, C, or L osteotomy; with bone graft (includes obtaining graft).
- Reconstruction of mandibular rami and/or body, sagittal split; without internal rigid fixation.
- Reconstruction of mandibular rami and/or body, sagittal split; with internal rigid fixation.
- Osteotomy, mandible, segmental.
- Osteotomy, mandible, segmental; with genioglossus advancement.
- Osteotomy, maxilla, segmental (e.g., Wassmund or Schuchard).
- Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant).
- Hyoid myotomy and suspension.
- Excision inferior turbinate (partial; complete excision produces the empty nose syndrome and should be avoided), any method.
- Submucous resection inferior turbinate, partial or complete, any method.
- Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft.
- Ablation, soft tissue of inferior turbinates, unilateral or bilateral, any method (e.g., electrocautery, radiofrequency ablation, or tissue volume reduction); superficial.
- Ablation, soft tissue of inferior turbinates, unilateral or bilateral, any method (e.g., electrocautery, radiofrequency ablation, or tissue volume reduction); intramural (i.e., submucosal).
- Glossectomy; less than one-half tongue.
- Fixation of tongue, mechanical, other than suture (e.g., K-wire).
- Tongue base suspension, permanent suture technique.
- Submucosal ablation of the tongue base, radiofrequency, 1 or more sites, per session.
- Unlisted procedure, palate, uvula.
- Pharyngoplasty (plastic or reconstructive operation on pharynx).
- Application of interdental fixation device for conditions other than fracture or dislocation, includes removal.
- Reconstruction midface, LeFort I; single piece, segment movement in any direction (e.g., for Long Face Syndrome), without bone graft.
- Reconstruction midface, LeFort I; single piece, segment movement in any direction, requiring bone grafts (includes obtaining autografts).
- Reconstruction of mandibular rami and/or body, sagittal split; with internal rigid fixation.

b. Tracheostomy

- Tracheostomy, planned (separate procedure).
- Tracheostomy, planned (separate procedure); younger than 2 years.
- Tracheostomy, emergency procedure; transtracheal.
- Tracheostomy, emergency procedure; cricothyroid membrane.
- Tracheostomy, fenestration procedure with skin flaps.

c. Hypoglossal nerve stimulation

Insertion and revision of the units implanted in different locations (chest and/or neck) may be needed, as specified by each device manufacturer.

Other treatment options (oral appliance therapy, positional therapy, weight loss, and upper airway reconstructive surgery) are available for select patients, although the treatment effect is frequently incomplete [54]. Upper-airway surgery, a treatment option for carefully selected patients with OSA, aims at reducing anatomical upper-airway obstructions in the nose, oropharynx and hypopharynx. However, long-term follow-up studies have suggested that the initial benefits of surgery may diminish over time [5]. Scant literature exists comparing invasive surgery and no treatment in OSA patients with inadequate adherence or failure to PAP systems [61,62].

Target population

[A0007] – What is the target population of this assessment?

Adult patients with moderate-to-severe Obstructive Sleep Apnea (OSA) who present inadequate adherence or failure to positive airway pressure (PAP) systems or to other non-invasive procedures.

[A0023] – How many people belong to the target population?

The available data make it difficult to determine the exact number of potential candidates for HGNS therapy who belong to the moderate–to-severe OSA subgroup of currently untreated patients. Moreover, data are lacking, as is the case with Austria [29]. In the absence of such data, a gross estimation could be made based on disease prevalence data.

OSA it thought to affect millions of people worldwide, and its prevalence is increasing due to higher incidences of obesity and an ageing population [44].

Large population-based prevalence studies of predominately white populations estimate the prevalence of OSA syndrome at approximately 3–4% in men and 2% in women [29]; non-symptomatic OSA is 3-5 times as common in the general population.

While OSA is not homogeneously distributed over age groups, and the exact natural evolution of the disorder is only partly known based on follow-ups of clinical cohorts and populations. Available data suggests that the disorder progresses slowly at least until the age of retirement [28].

In Australia, OSA is the most common chronic primary sleep disorder, affecting approximately 775,000 people in 2010 (4.7% of the population) [44]. In the Wisconsin Sleep Cohort Study, the prevalence of OSA, based on an AHI of >15 in people aged 30 to 60 years, was 9.1% in men and 4.0% in women [29].

[A0011] – How much is HGNS utilized?

Recent data estimate that about 5,500 implantations had been performed worldwide until June 2019 [31].

According to HealthPACT, in 2015, several HGNS trials were either underway or completed in the USA, Israel and 4 European countries: France, Germany, Netherlands, and Belgium [44]. In Australia, despite the fact that hypoglossal nerve stimulation devices are not registered with the ARTG

(Australian Register of Therapeutic Goods), diffusion of technology remains high and at least two clinical trials using the Apnex device have been undertaken in Australia. During the years 2011-2012, approximately 6,223 complete episodes of hospitalization (code E63Z in the AR-DRG system) constituted the recruitment pool for potential users of the device [44].

Introduction of the technology began in Sweden during spring 2015. However, the anticipated volumes of new, implanted devices was expected to be low (<5-10 cases annually) [28]. One year later, in March 2016, the Austrian Ministry of Health announced that 3 procedures had been performed in the past year and estimated an anticipated volume of 15 implanted HGNS devices per year (this information applies only to the applicants' hospital, data of expected frequencies for Austria are lacking) [29].

Concerns regarding the use of HGNS have increased markedly since 2015, and a number of countries have assessed or developed guidelines with recommendations for use of HGNS systems under the following conditions/circumstances:

Table 4-2: European and International Guidelines and Recommendations of Use

Country	Data	Document	Recommendation
Australia (HealthPACT) [44]	March 2015	A brief on Upper-Airway Stimulation for Moderate-to-Severe Sleep Apnea	- „...based on the lack of safety and clinical effectiveness evidence in the appropriate population, it is unlikely this device will diffuse into the jurisdictions within the next one to three years. It is therefore recommended that no further research on behalf of HealthPACT is warranted at this time" [29].
Sweden (HTA-centrum, Region Västra Götaland) [63]	2015	HTA on HGNS for treatment of OSA	- it emphases that HGNS treatment is expensive and further studies with long-term follow-up are needed.
Austria (LBI) [64]	2019	Decision support document for Upper Airway Stimulation for moderate-to-severe sleep apnea	- "...the inclusion in the catalogue of benefits is currently not recommended. The current evidence is not sufficient to prove that hypoglossal nerve stimulation for treating moderate-to-severe obstructive sleep apnea is more effective and equally safe than no treatment".
UK (NICE) [23]	November 2017	Interventional procedure overview of hypoglossal nerve stimulation for moderate-to-severe obstructive sleep apnea	- "Current evidence on the safety and efficacy of hypoglossal nerve stimulation for moderate-to-severe obstructive sleep apnea is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research".
Germany (German Society for Sleep Research and Sleep Medicine -DGSM) [65]	January 2017	German S3 Guideline Nonrestorative Sleep/Sleep Disorders, chapter "Sleep-Related Breathing Disorders in Adults," short version	"In the absence of anatomic abnormalities, neurostimulation of the hypoglossal nerve can be used in patients with moderate-to-severe OSA when positive airway pressure therapy meeting the abovenamed criteria cannot be employed. Neurostimulation should only be used in case of CPAP intolerance or ineffectiveness with AHI 15–50/h and ≤class I obesity, provided no concentric obstruction is documented in sleep endoscopy".
The Netherlands [66]	2017	Treatment of Obstructive Sleep Apnea	- „...it recommended to consider treating a patient with OSA with AHI between 15 and 65 who is CPAP intolerant with HGNS but do not treat a patient with HGNS if there is a BMI> 32, a complete concentric collapse at the level of the volume (with DISE), or more than 25% central apnea"
ECRI Institute [40]	June 2018	Technology assessment of the Inspire UAS therapy for treating OSA	- Available evidence suggests that use of Inspire is relatively safe and at least as effective as surgery for reducing nocturnal apnea and improving sleep and quality of life (QOL) in patients with OSA who cannot tolerate CPAP or BiPAP therapy or in whom it has failed. Limited data indicate benefits are sustained for 5 years. Findings are at high risk of bias and require further validation in

			prospective controlled studies of patients with typical OSA risk factors and comorbidities (e.g., obesity, age >65 years). Ongoing studies may partially address evidence gaps.
Blue Cross Blue Shield Association (BCBSA) - Evidence Street team [5]	2018 and January 2019	HTA; Surgical Treatment for Snoring and OSA Syndrome	- In selected patients, a positive assessment of Hypoglossal Nerve Stimulation (HNS) and an implicit recommendation for use are made.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of HGNS on mortality?
D0005	How does HGNS affect symptoms and findings (severity, frequency) of OSA?
D0006	How does HGNS affect progression (or recurrence) of OSA?
D0011	What is the effect of HGNS on patients' body functions?
D0016	How does the use of HGNS affect activities of daily living?
D0012	What is the effect of HGNS on generic health-related quality of life?
D0013	What is the effect of HGNS on disease-specific quality of life?
D0017	Were patients satisfied with HGNS?

5.2 Results

Effectiveness outcomes were rated by the Assessment Team and the clinical experts. The critical outcomes consisted of the AHI, ODI, hypoxemia time (percentage total sleep time with oxygen saturation < 90%), self-reported sleepiness and disease-specific quality of life using the Epworth Sleepiness Scale (ESS), quality of life (via the Functional Outcomes of Sleep Questionnaire FOSQ), overall mortality, cardiovascular events and adherence. Cerebrovascular events were rated as an important outcome.

Table A10 in Appendix 1 summarizes the GRADE quality assessment, its effect and importance, with a quality rating for each outcome.

Included studies

Only one comparative study was identified, a randomized controlled therapy withdrawal study [22] that assessed the effectiveness and long-term durability of the effects of the Inspire® Upper Airway Stimulation System (UAS) (Inspire Medical Systems, Inc.). The first 46 patients who had been successfully treated with UAS therapy one year after device implantation from a phase III trial cohort (Stimulation Treatment for Apnea Reduction, the STAR trial) were randomized to have their device turned ON or OFF during a 1-week period. Subsequently, all returned to using the UAS device and were followed-up for an additional six months. The two groups were compared with regard to objective sleep and respiratory parameters as well as subjective sleep-related quality of life variables. A paired *t* test was used to evaluate the difference of change from 12 and 18 months to RCT between the 2 groups. Similar comparisons for other outcome measures were made within each group and between the 2 groups at baseline, at 12 months, at the RCT 1-week window and at 18 months.

In addition, six prospective single-arm studies were retrieved to obtain information regarding mortality and treatment adherence. The ADHERE registry [17,19,21] provided results on hours of daily device use. Within the framework of the STAR trial [15], data on self-reporting use, as a percentage of the subject's adherence to treatment at follow-up, were also communicated.

Mortality

[D0001] – What is the expected beneficial effect of HGNS on mortality?

This question is not addressed in the selected RCT. No comparative evidence was found regarding overall mortality. There is no available evidence regarding the expected beneficial effects of HGNS on mortality. The only RCT (therapy withdrawal) from the STAR trial did not collect adverse events. In any case, neither the RCT nor the observational single-arm studies reported any death-related data in terms of the procedure or the device.

Morbidity

[D0005] – How does HGNS affect symptoms and findings (severity, frequency) of OSA?

Apnea hypopnea index (AHI). Outcome rated as critical.

The RCT conducted by Woodson et al. [22] reported significant changes in AHI after one week with or without activation of the UAS Inspire® (Inspire Medical Systems, Inc.) device. The study included 23 patients in both groups, using an ON-OFF protocol. One week after randomization, the ON group showed a slight change in their AHI score (a mean increase of 1.7 $\pm$ 6.4 SE), while a significant increase was observed in the OFF group (18.2 $\pm$ 15.6 SE). Namely, the value of the AHI increased, returning to baseline levels, which indicated a worsening of the condition. The mean difference of change between ON-OFF was 16.4 (9.2, 23.7 CI 95%, *P* value <.001). All patients then returned to using the device and were followed-up for an additional 6 months, until a total of 18 months of follow-up was completed.

At 18 months the AHI scores of the OFF group again decreased, returning to low levels, while the ON group maintained their low levels throughout this same time period; mean difference (ON-OFF, 95% confidence level) of 0.2 (-5.1, 5.4) with a P value of 0.69.

Oxygen desaturation index (ODI). Outcome rated as critical.

Regarding ODI, a significant difference between ON and OFF was also observed. One week after randomization the ON group showed a slight change in their ODI score (a mean increase of 1.6 + 5.8 SE), while a significant increase was observed in the OFF group (17.0 + 14.5 SE). Similarly, as with AHI, the return to baseline values in the OFF group indicated a worsening of the symptoms. The mean difference of change between ON-OFF was 15.4 (8.7, 22.1 CI 95%, *P* value <.001). At 18 months both groups reported ODI levels similar to those reported at 12 months (just before randomization).

Hypoxemia time (percentage total sleep time with oxygen saturation < 90%). Outcome rated as critical.

In the case of Hypoxemia Time, significant differences were observed between ON and OFF. The mean difference of change between ON-OFF was 5.4 (0.1, 10.7 CI 95%, *P* value 0.04).

No evidence was found regarding cardio/cerebrovascular morbidity, as no study addressed this outcome.

[D0006] – How does HGNS affect progression (or recurrence) of OSA?

According to Woodson et al. [22], withdrawal of UAS therapy leads to a rapid recurrence of OSA, associated with daytime sleepiness symptoms and impaired quality of life, similar to withdrawal of nasal CPAP. The comparison between two randomized groups with therapy ON versus OFF in the current study demonstrated that withholding therapy for one week led to a return of disease severity to baseline levels without clear evidence of disease modification. Subjects needed to maintain UAS therapy to obtain sustained efficacy, similar to CPAP.

[D0011] – What is the effect of HGNS on patients' body functions?

No evidence was found to answer this research question.

[D0016] – How does the use of HGNS affect activities of daily living?

No evidence was found to answer this research question.

Health-related quality of life

[D0012] – What is the effect of HGNS on generic health-related quality of life?

No evidence was found to answer this research question.

[D0013] – What is the effect of HGNS on disease-specific quality of life?

Epworth Sleepiness Scale (ESS). Outcome rated as critical

Normal ESS is a score of 10 or less. The ON group remained in the normal range one week after randomization, while the OFF group worsened their ESS levels. The modification expressed as the difference of change from 12 months to RCT (mean difference, ON – OFF, 95% confidence level) was 4.2 (2.0, 6.4) with *P* value <.001.

At 18 months, with the device activated in all patients, both groups had similar scores; mean difference ON-OFF at 18 months of -2.0 (-4.5-0.4 CI 95%), *P* value 0.09.

Functional Outcomes of Sleep Questionnaire; FOSQ. Outcome rated as critical

Normal FOSQ is defined as a score greater than 17.9. The ON group remained within the normal range one week after randomization, while the FOSQ levels of the OFF group worsened. The modification expressed as the difference of change from 12 months to RCT (mean difference, ON – OFF, 95% confidence level) was –2.3 (–3.8, –0.9) with a *P* value of 0.001.

At 18 months, with the device activated in all patients, both groups recorded similar FOSQ scores; mean difference ON-OFF at 18 months was 0.9 (–0.8, 2.6) with a *P* value of 0.29.

The clinically meaningful differences for ESS and FOSQ were not formally defined, although the authors concluded that their results demonstrated no difference between the two groups at that time. Self-reported measures, such as ESS and FOSQ, showed no difference between the 2 groups at 12 and 18 months with therapy activated but reverted to baseline in the therapy OFF group at the RCT assessment.

Satisfaction

[D0017] – Were patients satisfied with HGNS?

No evidence from comparative studies was found to answer this research question. However, data on treatment adherence is available from non-RCT prospective studies.

In the framework of the ADHERE registry, Thaler et al.[21] reported that in following-up 382 patients over 12 months the median device report of objective therapy use was 5.7 (IQR, 4.1–7.1; mean, 5.6 ± 2.1) hours per night. They also found that female participants had a mean therapy use of 5.9 ± 2.1 hours per night and males 5.5 ± 2.1 with a P value of 0.18. Likewise, Hofauer et al. [19] in a study involving 102 patients reported an objective therapy usage of 5.7 hours (± 2.0) daily (on average 40.0 hours per week (± 14.2)) and subjective reports of 6.8 nights of use per week. Elderly patients revealed a better adherence to the stimulation therapy. Steffen et al. [17] reported a nightly voluntary use of the device of 6.1 hours per day in 56 patients.

In the STAR trial, Woodson et al. [15] informed a self-reporting nightly device use of 86%, 81%, and 80% at years 1, 3, and 5, in 124, 123 and 97 patients, respectively.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is HGNS in relation to comparators?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	Which are the susceptible patient groups that are more likely to be harmed through the use of HGNS?
C0007	Are HGNS and its comparators associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of HGNS and its comparators?

6.2 Results

Safety outcomes were rated by the Assessment Team and the clinical experts. All serious adverse events were rated as critical outcomes, as well as the non-serious events related to device use. Non-serious adverse events associated with the procedure were rated as important outcomes. Table A11: in Appendix 1 summarizes the GRADE quality assessment, as well as the effects and their importance, with a quality rating for each outcome. Outcomes are presented in separate sections by seriousness and time of follow-up. The events were classified as serious or non-serious according to the classification provided by the study authors. Short-term follow-up was defined as that lasting up to 12 months; in the second group, the follow-up period was longer.

Included studies

Six studies were included in the safety analysis, all of which were non-comparative and prospective. These studies encompassed a total of 1,307 implanted patients; safety results were followed-up for at least 6 months in 928 of the patients. The six studies were as follows: the STAR trial [15], the THN2 trial [20], the G-PMS trial [17], ADHERE [21], UAS [16], and the BLAST-OSA [18]. Five of the 6 studies reported adverse events in 868 patients during the first year of follow-up (visits at 6/12 months), while 2 of the studies reported new adverse events in 157 patients during subsequent years (up to 5 years of follow-up). The 2014 RCT of Woodson et al. [22] did not include safety data among its outcomes, nor did it report adverse events.

The largest series was the ADHERE, which evaluated the HGNS produced by Inspire Medical Systems, Inc. [21]. ADHERE involved 640 patients who completed the 6-month visit and 382 a 12-month visit. The STAR Registry [15] reported safety data on the Inspire Medical Systems HGNS for 124 patients at 12 months, and for 97 patients at 60 months. Safety results for the aura6000™ device are derived from a study of 46 patients with 6 months of follow-up. The Genio™ device results are based on 27 patients followed-up for 6 months. Finally, the results of Apnex are drawn from 31 patients with 12 months of follow-up. Table A5 summarizes the safety outcomes of the included studies.

Patient safety

[C0008] – How safe is HGNS in relation to comparators?

No comparative studies were found to answer this question. The only RCT (sham control) from the STAR trial did not collect adverse events data. Moreover, the evidence available does not allow for comparing the devices in terms of safety.

The six studies included in the safety assessment were all prospective single-arm studies that reported safety results with a follow-up period of 6 months or longer for a total of 928 patients. Five of the six studies provided safety data with a follow-up period between 6 and 12 months for 868 patients. We gathered safety information with longer follow-ups (36-60 months) from two studies; one of them only provided information for 60 patients after a follow-up period of 36 months. The other study provided data at 12 and 60 months of follow-up.

The number of AEs reported for those 928 patients was 949. Taking into account that a patient could have more than one AE, there was an average of 1.02 events per patient (see Table 6-1). The percentage of patients that suffered AEs could only be calculated for serious AEs. Among the 928 patients, 32 suffered a serious AE; thus, the percentage of patients that suffered a serious AE was 3.45%.

Five out of the six studies reported 768 adverse events for 868 patients during the first year of follow-up [15–18,20,21], which is an average of 0.88 AEs per patient in the first year. In subsequent years (from 1 to 5 years of follow-up), patients presented, on average, 1.15 adverse events.

There were 35 serious adverse events in 32 patients, 20 of them being device related (see Table A5). Among the serious device-related AEs, most were surgical interventions for explantation or device modification. There were 6 explantations in 5 patients due to infection (4 cases) and lack of effectiveness (2 cases). There were surgical interventions for replacement/repositioning on 20 occasions in 19 patients. Other serious adverse events were procedure related, such as infections, pain, bleeding and impaired swallowing that required prolonged hospitalization.

Regarding non-serious adverse events, although 914 were reported, it was not possible to ascertain the number of patients that suffered such events across all of the studies. Among the non-serious events, 580 were device related, the most frequent being tongue abrasion, mild pain or discomfort related to the device, insomnia/arousal and device usability complaints.

The most frequent non-serious procedure-related AEs were complications associated with incisions such as hematomas, swelling, and numbness. Other frequent non-serious procedure-related AEs were infections, pain, impaired swallowing, tongue weakness, dysarthria, intubation adverse effects and other post-operative mild symptoms.

No deaths associated with the procedure or device were reported.

Detailed results and explanations are shown in Table 6-1 (frequency and severity of adverse events), Table A5 (results summary for safety outcomes) and Table A11**:** (SAFETY GRADE assessment).

[C0004] – How does the frequency or severity of harms change over time or in different settings?

We did not find comparative evidence to properly address this research question.

The prospective single-arm studies yielded information regarding frequency and severity. For example, a patient could present more than one adverse event. On average, the number of adverse events per patient during the first year was 0.88 (five out of the six studies reported 768 adverse events for 868 patients) [15–18,20,21]. In subsequent years (1 to 5 years of follow-up), there were 181 new adverse events in 157 patients. Hence, on average, a patient presented 1.15 adverse events. According to the information available, the frequency of AEs was lower during the first year of follow-up, although the evidence does not allow for comparing periods of time or for distinguishing factors that might determine differences over time.

[C0005] – Which are the susceptible patient groups more likely to be harmed by the use of HGNS?

We did not find any evidence to properly address this research question.

Only one study [67] (excluded from the analysis since its results had been included in a larger study) analysed results according to age. In this study, older (>65 years) and younger (<65 years) patients showed no differences in terms of major adverse events related to differences in age. No other susceptible patient groups were analysed in the retrieved literature.

[C0007] – Are HGNS and comparators associated with user-dependent harms?

We did not find evidence allowing for a comparison of user-dependent harms between HGNS and comparators.
Examining single-arm studies we found that a significant number of adverse events reported in the six studies involved usability complaints (130 of 949 AEs). In the longest series [21], the most frequent AE was discomfort related to stimulation (69 of 272 AEs).

[B0010] – What kind of data/records and/or registry is needed to monitor the use of HGNS and comparators?

Records and registries proved to be similar to the trials found in the literature. A German post-market registry [17] and a sub-investigation [19] of the same collected long-term data on implanted patients. Pre-intervention data included previous AHI measurements, with home sleep test (HST) and the effectiveness of drug-induced sleep endoscopy (DISE) used to characterize the collapsibility of the velum and nature of outcomes. In these studies, the collected data included effectiveness outcomes obtained through polysomnography and data directly downloaded from the device, in addition to questionnaires on health-related quality-of-life issues and adherence data. Adverse events, both serious and non-serious, which had already been established in the trials found in the literature, had to be collected on a patient-by-patient basis. Suggestions on blood pressure and cardiovascular data collection are detailed in the DISCUSSION

Table 6-1: Frequency and severity of adverse events in prospective series (No comparative data available) [15–18, 20, 21]

	Serious adverse events No of events (events per patient)		Non-serious adverse events No of events (events per patient)		928 patients**
	1st year of follow-up 868 patients	Subsequent years[a] 157 patients	1st year of follow-up 868 patients	Subsequent years[a] 157 patients	
Device-related adverse events					
Device explantation due to failures	2				2
Device replacement/reposition due to failures	7	11			18
Discomfort/mild pain due to the device			184	68	252
Device-related infections			1		1
Tongue abrasion			75	21	96
Tongue fasciculation			4		4
Dry mouth			10	10	20
Device usability complaint			83	47	130
Insomnia/arousal			27		27
Paresis, paraesthesia			11		11
Other acute device-related symptoms			21	18	39
Procedure related adverse events					
Infection that led to device explantation	4				4
Infection without device explantation			7		7
Pain (2 cases with device replacement)	3		19		22
Bleeding, severe hematoma	2				2
Impaired/painful swallowing	1		13		14
Tongue weakness			37		37
Dysarthria			7		7
Intubation effects, anaesthesia complications			19		19
Discomfort related to incisions, hematoma, swelling, numbness, abnormal scarring			98	5	103
Other postoperative mild symptoms, headache, discomfort			128	1	129
Others	5				5
Total Number of adverse events	24 (0.03)	11 (0.07)	744 (0.85)	170 (1.08)	949 (1.02)

a From 12 to 60 months of follow-up. The short-term events reported were not included in the long-term follow-up. **97 patients were included both in the first year and in subsequent years of follow-up.

7 POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

7.1 Research questions

Two questions were considered relevant to this chapter. Does the introduction of HGNS and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues? Does comparing HGNS to the defined, existing comparator(s) reveal any differences that may be organisationally relevant?

To answer the checklist for potential ethical, organisational, social and legal aspects, we used information drawn from the literature search and the Assessment Team's consensus-based opinion. The checklist summarizes our judgment that there might be ethical, organisational and legal aspects that the users of this report may wish to consider further. It was not our objective to undertake an extensive search of the literature to provide a comprehensive overview for each ethical/legal aspect relating to the use of HGNS. These and other questions included in the “Checklist for potential ethical, organisational, social and legal aspects” can be perused in Appendix 3.

7.2 Results

Does the introduction of HGNS and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?

We could not find specific evidence to properly address this question. However, the introduction of this new technology could involve ethical issues if equal public access is not achieved. In order to avoid equity barriers, more studies that might better define which populations could most benefit from use of the technology are needed.

Does comparing HGNS to the defined, existing comparator(s) point to any differences that may be organisationally relevant?

Although no specific literature was found that might comprehensively compare this new technology against the standard of care in terms of organisational issues, it is reasonable to assume there might exist implementation issues; e.g., learning curves and requisite skills for conducting HGNS. Implementation of this technology will require specific training not only for health care professionals, but also for patients.

8 PATIENT INVOLVEMENT

As explained earlier, patient involvement was pursued during the scoping phase. Patients who matched the population target characteristics, including those with experience using the device, were sought via clinical experts and organisations. After several contacts with individuals and patient organisations, four patients were contacted, with one of them finally agreeing to participate in the assessment.

The patient signed a declaration of interest and confidentiality undertaking form (DOICU) and participated. The process to obtain patient input was “one-on-one conversation” through a semi-structured interview.

A verbal informed consent was obtained before carrying out the telephone interview. A summary of the answers was validated by the patient and feedback about the process was obtained.

Patient input was found relevant for the scoping phase, to include their experience living with the disease and with the device under evaluation. This feedback was collected and discussed within the scoping phase - including during the scoping meeting - with the assessment team and the clinical experts.

The patient's validated summary of the interviews are recorded below.

Patient interview

This is a summary of the interview conducted with an individual patient, not associated with any patient organisation, who agreed to participate on his/her own.

A verbal consent for the interview was obtained, and the below provides a validated summary of the patient input.

Said patient is 40 years old, and has been living with the condition for at least 20 years, although he was clinically diagnosed only in 2004, when he was 24. He had gained some weight after giving up smoking and his family was also affected by OSA.

Describing his condition, he remembers that he suffered constant headaches during the day (“It was like having a hangover all the time”), tiredness (“it was horrible to do anything”) and falling asleep at any place or time during the day. He says that it was a “very difficult time in his life”. His condition was affecting his daily life, his work, and his relationships, including his wife, who acted as a caregiver, always vigilant of his sleep patterns.

He needed three alarm clocks in the morning to wake up, as well as calls from his wife. His sleepiness made him suffer several frights; e.g., when he fell asleep while driving on one occasion, fortunately without consequences.

All of these circumstances led the patient to a situation he described as a “parallel way to live his life”, with increasing loss of interest for everything, de-socialization and home confinement, fatigue, emotional limitations, and finally depression.

The condition was clearly impacting the patient’s quality of life. When he was diagnosed in 2004 with severe OSA, with an Apnea-Hypopnea Index (AHI) of 40 events/hr., the initial treatment consisted of a CPAP device in conjunction with surgery to the nasal septum. In 2007 a further surgery was carried out, this time a palatoplasty.

Years passed with a slight improvement, but not nearly enough for the patient; he still experienced symptoms and his quality of life was not improving. When asked what it was like to use the CPAP, he said “that it was so uncomfortable, that it was not a solution”, and quantified his satisfaction with it as “55%”, considering it “a temporary fix” since he was continuing to experience symptoms, albeit less severe than before. He remembers bloating, and flatulence as one of the adverse effects. In 2013 another intervention was undertaken, this time with a septoplasty and the removing of some tissue from the palate, which somewhat helped his condition.

Over the years he had sought the opinions of several different physicians, including treatments in different countries. For some time he considered undergoing maxillomandibular osteotomy and maxillomandibular advancement surgery.

In 2014 he had reached the point where “he would do anything, even an experimental treatment” to improve his symptoms, his disease, his quality of life.

He was told of a new treatment, the device under evaluation in this report, and after being provided an explanation, videos and other information from his otorhinolaryngologist he decided to try the new technology.

He would undergo the surgery, with follow-up procedures at 6 months and then at 1 year.

He remembers the surgery as “not problematic at all” and a huge change from that moment forward (“this changed my life”). For him, the device is easy to use, and to carry when traveling. He also feels it lends him more autonomy since “you only have to manage a remote, pausing it without problem if for some reason you wake up”. He considers the device **not only easier** to manage in every way than the CPAP, **but also noticed positive effects from day one.** The implant has not entailed any difficulties for him, though he must exercise “the normal care to not to hit or receive a hit in the exact location”.

His life returned to normal, **or more exactly to what it should have been**, with his family and his work life (avoiding only extreme sports), and his quality of life has improved (“I didn’t feel this tranquillity before”). He no longer experiences symptoms, sleeps well, and the depression has disappeared. In fact, if forced to choose the worst symptom he experienced, he is categorical in his reply: “depression”.

The patient has been using the device for 3 years now. When asked how the technology could be improved, he says that perhaps it could be made smaller **even though it does not disturb him in any way, and hopes the battery life** will have a longer duration (10 years is the current **estimate**), as well as to be more affordable.

When asked for key messages he offered the following:

On symptoms: “Depression, was the worst part of my disease, it tore me apart **as well as my family and wife”; it's a disease that causes all surrounding family members to suffer as well.**

On treatments: “Talking to some people I am related to, they say that CPAP is very uncomfortable and **difficult to stand on a daily basis, the overall issue I recollected from CPAP is the lack of success and results to help me through that illness; all aspects were very negative".**

On the device: “I would gladly recommend it, especially to those who cannot tolerate the CPAP. I would like to help others in my situation, and decision-makers through my own experiences.”

9 DISCUSSION

9.1 Discussion of the methodology

Discussion of the search strategy

As stated in the project plan, a predefined search strategy with controlled terms and free text in the main databases was followed. Manual searching complemented this strategy, in order to avoid missing any study relevant to the inclusion criteria. No specific search strategy was developed for the CUR or TEC domains. No information regarding one of the devices was obtained even after several contacts with the manufacturer (Nyxoah).

Discussion of the inclusion and exclusion criteria

Due to the lack of large clinical trials with a control group, observational studies were also accepted for inclusion in the effectiveness analyses of outcomes that would require a longer follow-up period: adherence, quality of life, mortality and cerebrovascular events. Only prospective studies with data on more than 10 patients were accepted for this deviation from the project plan.

A specific software (Rayyan QCRI) was utilized by two independent reviewers to classify the studies obtained during the search [68]. Those studies that could not be evaluated based only their abstracts were retrieved in full text versions to reach a final decision. When a conflict occurred between the two reviewers, a third reviewer took part in the discussions for final classification. Editorials, letters and congress communications in which an analysis of the quality of evidence or additional follow-up data was not possible were excluded. We tried to contact authors in those cases where additional data was deemed necessary. When no answer was forthcoming, this was noted and the study discarded. When a study had been updated, the most recent publication was included in the analysis.

No systematic reviews were included due to differences in inclusion criteria, objectives and/or non-use of the GRADE methodology.

Discussion of the quality of evidence

Rating of the outcomes using GRADE methodology was done by the Assessment Team (authors, co-authors, dedicated reviewers) and clinical experts during the scoping phase. None of the outcomes was rated as not important. Regarding effectiveness, the AHI, the ODI, the % of sleep time with oxygen saturation level below 90%, the ESS, the Quality of life, overall mortality, cardiovascular events and adherence to treatment were rated as critical. Only two effectiveness outcomes were rated as important, the occurrence of cerebrovascular events and technical and procedural success. As explained earlier, the latter was excluded from the analysis. The authoring team decided to remove this outcome based on suggestions from the Assessment Team. The risk of indirectness due to surrogate outcomes such as AHI or ODI was noted in the GRADE assessment, which resulted in a downgrading of the quality of the outcomes as well.

In the case of safety outcomes, serious adverse events were classified as critical. Among the non-serious adverse events, those related to the device were classified as critical, while those related to procedure were classified as important.

The Revised Cochrane risk-of-bias tool for randomized trials (RoB-2) was utilized for the only comparative study, a RCT withdrawal study that posed a high risk level. Detailed scoring is provided in Table A7 and Table A8.

The quality of the single-arm studies was evaluated using the IHE checklist as shown in Table A9.

The quality of the evidence was found to be very low not only for the non-comparative study, but also for the controlled study. A high risk of bias was also noted as there was no description of the randomization method, there was a lack of blinding and, no intention-to-treat approach was included. In addition, the sample consisted of only 23 patients per group, there was only a week of intervention, and the evaluation of patients was based on polysomnography results. The latter, although a key outcome for this field, is still a surrogate outcome.

The quality rating could not be improved. This was due to the large effect at work, a plausible confounder that might alter the effect, or a dose-response gradient.

All of these factors are noted in the GRADE tables. Conflicts of interest, resources and funding information are detailed for all studies.

Limitations of the studies

There are some limitations to the analyses of the data. The fact that some studies contain data from the same registries at different time points increases the likelihood that some overlapping of patient data occurred. Although some follow-up periods were clearly defined, others were mixed; thus, it was not possible to confirm whether some of the same patients were being followed-up in other studies. The durations of the follow-up periods were short and mid-term, with only two studies containing long-term results.

Another limitation was the variability in the reporting of adverse events; similar definitions were adopted, but the recording of adverse events was heterogeneous. For example, it was unclear in some cases how many patients had their events reported, and at which time these events were occurring.

Lastly, a publication bias could not be discarded since data from the ADHERE registry and the STAR trial did not encompass the entire spectrum of settings under which HGNS was performed. The ADHERE registry comprised 600 of the 3000 patients who had been treated with UAS as of April 2019 [67].

Discussion of the analyses and results presentation

GRADE tables on effectiveness and safety outcomes were constructed. As per the project plan, the comparator's only setting consisted of having the device disconnected. The decision not to include CPAP or surgical approaches as comparators was made during the scoping phase and in accordance with the project plan. The rationale for doing so is that although CPAP is the first-line therapy for moderate-to-severe obstructive sleep apnea, a control group of therapeutic CPAP users would prove impractical since only those who could not use it (non-responders or because of inadequate adherence), or who declined to do so, constituted the target group of the intervention of interest (UAS) [2,29,69]. A variety of surgical approaches such as anatomical restructuring are being used in a very limited number of carefully selected patients, although they represent a very small population and such surgery is not an adequate comparator for HGNS.

The analysis was conducted in keeping with the design of the studies, separating the results from observational studies from those of comparative ones.

Outcomes that could not be assessed with comparative data were evaluated through observational studies, taking into account the risk of bias. The largest prospective study was used for a safety

assessment and involved 640 patients for 12 months of follow-up [21]. The longest follow-up study included 97 patients over 60 months of follow-up [15].

For purposes of analysis, we classified the adverse events into two categories: serious and non-serious. This was possible since both studies defined it similarly. Procedure-, device- and unrelated adverse events (serious and non-serious) were analysed at 12 months and from months 12 to 60. This was done to avoid any underestimation of events since the number of patients followed-up for more than 12 months was very low compared to the number that completed 12 months of follow-up. The reason for not using the additional cut-off point of 6 months was the impossibility of differentiating this time period for the reported adverse events. Among the various studies, we found it difficult to separate the periods when the serious events happened, particularly in cases where they were reported heterogeneously.

9.2 Discussion of effectiveness and safety

Discussion of effectiveness

According to Woodson et al. [15], withdrawal of HGNS led to a rapid recurrence of OSA severity, daytime sleepiness, and impaired quality of life. At 18 months, with the therapy ON in both groups, outcome measures had returned to within normal ranges.

This study suggests that use of HGNS led to a reduction of OSA severity and improved quality of life.

In a randomized withdrawal trial, subjects receiving a test treatment for a specified time period were randomly assigned to continue treatment either with the test treatment or with a placebo (i.e., withdrawal of active therapy). Any difference that emerged between the group receiving continued treatment and the group randomized to placebo would demonstrate the effect of the active treatment. It is also important to realize that the treatment effects observed in these trials could have been more pronounced than those in an unselected population, as randomized withdrawal studies are enriched with responders and exclude subjects who cannot tolerate the treatment [70]. The limitations of the selected study were particularly remarkable in that there was no information about randomization methodology and that the evidence was drawn from highly selected participants; i.e., those who had previously responded positively to the therapy (UAS responders). In addition, the evidence was derived from only a single RCT with a small sample size; thus, the possibility of bias must be carefully taken into account.

No comparative evidence related to HGNS treatment adherence was found in the efficacy assessment, although data for this outcome was found in the non-RCT studies, recording a high number of hours per night of self-reported use. The largest prospective study of HGNS identified by us, involving 382 patients, reported a median use of 5.7 hours per night with 12 months of follow-up [21]. When CPAP adherence was defined as more than 4 hours of nightly use, 46 to 83% of patients with OSA have been reported to be non-adherent [23-25]. Data from non-RCT studies indicated a level of device use that exceeded the earlier reported CPAP adherence, although additional evidence is needed to support any firm conclusions on this issue.

Although no evidence was found regarding the influence of variables such as age and sex on the effectiveness of HGNS, some findings reported by the non-RCT studies warrant mention. Elderly patients showed better adherence to HGNS therapy [19]. In addition, a statistically significant improvement and higher use rate in female patients was found [21]. Although the ADHERE study cohort's average age of 60 years might appear high, age as an independent variable did not predict response. In fact, self-selection of patients that skewed the population older may have been at work.

The exact reason for the increased usage among females and older patients is unclear. In any case, these findings warrant further investigations. Hence, the clinical importance of these data is uncertain at this time.

Therefore, on the basis of the evidence extracted from the selected RCT, the greater efficacy of HGNS compared to no treatment cannot be stated with confidence.

Discussion of Safety

The single comparative study available did not report any safety results; thus, the safety information was drawn from prospective single-arm studies. This implies that there is no evidence to determine whether HGNS is safer than other technologies. Moreover, the available evidence does not allow for any comparisons among the four devices in terms of safety.

Furthermore, adverse events were not clearly reported in some studies. It was impossible to calculate the percentage of patients that suffered adverse events in all studies. Indeed, this could only be determined for severe AEs.

The available information indicated a significant number of non-serious adverse events, and a lower frequency of serious adverse events. The latter were those that lead to surgery, severe conditions or life-threatening situations, although there were no deaths related to either the procedure or the device.

The most frequent serious adverse events were surgical interventions due to replacement or repositioning of the device (23 interventions). Explantation was carried out in 6 patients, most of them due to infection.

The most frequent adverse event was discomfort/pain related to the device. The second most frequent were device usability complaints. The majority of reported adverse events were device related (600 of 949 AEs). It is important to realize that several adverse events were sometimes attributable to a single patient.

Tongue abrasion, pain associated with the presence of the device, paresis, paraesthesia, insomnia or arousal, and other complaints associated with the device were frequently reported. Although these conditions were not life-threatening, it is clear that some patients suffered several of them at once.

Regarding loss of patients to follow-up, this mainly occurred in just one study and no information regarding the reasons for discontinuation was provided. Among the 1,307 patients in whom a device was initially implanted, 380 (29.07%) were lost before the first follow-up visit (these were generally scheduled 6 months after implantation). In the ADHERE Registry [21], 377 of 380 patients did not keep their 6-month appointment, although no reason was stated for this lack of information. Of the other 3 patients, 2 requested explantation of the device and 1 died because of a cardiac event not related to the intervention.

The selected studies do not give an accurate accounting of losses to follow-up. The reporting of effectiveness and safety was based on the protocol approach, not on intention to treat, which could bias the results.

Ideally, it would be worthwhile to assess whether or not and to what degree multiple events, and at different times, might affect a patient's adherence to the device, although in these responders adherence appears to have bene maintained. Unfortunately, data regarding this aspect is only short-term in nature [69,70]. In addition, impacts on specific aspects of quality of life could not be determined based on the data from these trials.

Longer term data is needed to establish the evolution of adverse events over time. Discomfort due to electric stimulation, tongue abrasion or arousal were diminished with careful adjustment of the device's functional parameters [15]. Some authors reported that disruptive sensations could be ameliorated over time [18], although longer follow-up periods involving larger patient cohorts would be needed to confirm this.

The evidence gathered does not allow for safety comparisons among the devices. In any case, most of the studied patients were treated with the HGNS produced by Inspire Medical Systems Inc. Among the 928 patients with follow-up safety data, 824 (88.8%) were treated with Inspire's HGNS. In addition, the longest follow-up periods were also of patients treated with this device.

Imthera's aura6000™ provided safety results for 46 patients and Genio™ System for 27 patients. The other device, HGNS® Apnex Medical, was withdrawn from the market. We included in our review the first trial that published results from APNEX's device (31 patients followed-up for 12 months) [15]. This study was followed by a larger scale phase 2-3 clinical trial, which apparently failed to yield the expected results: the AHI fell from 45 to 25 as a mean, slightly less than the expected 50% decrease. This led to a halt in the development of the device and closure of APNEX [69]. In any case, removal of this study did not alter the findings of this report.

Lastly, case reports were not included in the analysis, and although electrical stimulation by other concomitant devices, such as implantable cardioverters, appears to be safe, some interferences with external electric stimulation (e.g., cardioversion) have been described [71]. In contrast, electroconvulsive therapy did not interfere with a device in another study [72]. Other serious adverse events, such as pneumothorax [73], were not reported in the analysed trials.

10 CONCLUSIONS

The comparative effectiveness among HGNS devices versus no treatment is based on only one small and low-quality randomized controlled study involving the Inspire® Upper Airway Stimulation System (UAS). This study was conducted with a group of selected patients, those who positively responded to that particular UAS device. Thus, it is not applicable to the whole population of interest.

This study found significant worsening in such clinical intermediate outcomes as the Apnea Hypopnea Index, the Oxygen Desaturation Index and the Hypoxemia Time when the device had been disconnected for one week.

Regarding quality of life (ESS and FOSQ scores), there was a significant worsening after one week when the device was in deactivated mode compared to the group with the device in activated mode.

Neither the RCT nor the observational single-arm studies reported any deaths related to the procedure or the device.

Although no comparative evidence was found regarding adherence, the largest single-arm study found a median device use of 5.7 hours per night in 382 patients after 12 months of follow-up.

No evidence was found regarding the following critical outcomes: cardio/cerebrovascular morbidity and long-term effects on quality of life.

As the RCT did not address safety outcomes, the available evidence does not allow for any conclusions to made as to whether HGNS is safer than no treatment in the population of interest. Although information from prospective single-arm studies was retrieved and analysed, the quality of evidence regarding safety proved to be very low.

A significant number of device- and procedure-related adverse events were reported. An average of 1.02 adverse events per patient was reported and 3.45% of patients suffered a serious adverse event. The most frequent serious adverse events were surgical interventions due to replacement, and repositioning or explantation of the device. The most frequent non-serious adverse event was discomfort/pain related to the device.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Database: Ovid Medline ® 1946 to present
Search date: 2020-01-22

#	Search	Hits
1	Sleep Apnea Syndromes/	14399
2	Sleep Apnea, Obstructive/	19312
3	(sleep adj4 (apnoeaapnea or apnea or hypopnea or hypopnoea)).ti,ab,kw.	35512
4	(sleep adj4 disorder* adj4 breath*).ti,ab,kw.	7698
5	(sleep-disorder* adj4 breath*).ti,ab,kw.	6251
6	(upper adj4 airway adj4 resistance adj4 syndrome).ti,ab,kw.	254
7	(OSA or OSAS or OAHS RO OSAHS).ti,ab,kw.	17126
8	1 or 2 or 3 or 4 or 5 or 6 or 7	46364
9	((hypogloss* or geniglosusu) adj4 (stimul* or neurostimulat*)).ti,ab,kw.	319
10	(cranial adj3 (XII or XIIs or twelfth) adj4 (stimulat* or neurostimulat*)).ti,ab,kw.	5
11	(tongue adj4 neurostimlat*).ti,ab,kw	5
12	Electric Stimulation/	113126
13	Electric Stimulation Therapy/	20183
14	(electric* adj4 (stimulat* or neurostimulat*)).ti,ab,kw.	64371
15	electrotherap*.ti,ab,kw.	2193
16	(electrostimulation adj3 therap*).ti,ab,kw.	126
17	(upper adj4 airway adj4 stimulat*).ti,ab,kw.	212
18	(upper-airway adj4 stimulat*).ti,ab,kw.	209
19	(sleep adj4 therap* adj4 system*).ti,ab,kw.	34
20	Implantable Neurostimulators/	560
21	(implant* adj3 (stimulat* or neurostimulat*)).ti,ab,kw.	4384
22	inspire.ti,ab,kw.	4469
23	aura6000.ti,ab,kw.	0
24	Imthera.ti,ab,kw.	5
25	Nyxoah.ti,ab,kw.	2
26	(Genio adj3 (system* or Device)).ti,ab,kw.	2
27	(HGNS adj2 system).ti,ab,kw.	6
28	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	165995
29	8 and 28	533

Database: EMBASE Elsevier 1947 to present
Search date: 2020-01-22

#	Search	Hits
1	'sleep disordered breathing'/exp	76996
2	(sleep NEAR/4 (apnoea OR apnea OR hypopnea OR hypopnoea)):ti,ab,kw	61634
3	(sleep NEAR/4 disorder* NEAR/4 breath*):ti,ab,kw	14222
4	('sleep disorder*' NEAR/4 breath*):ti,ab,kw	11741
5	(upper NEAR/4 airway NEAR/4 resistance NEAR/4 syndrome):ti,ab,kw	426
6	#1 OR #2 OR #3 OR #4 OR #5	83346

7	((hypogloss* OR geniglosusu) NEAR/4 (stimulat* OR neurostimulat*)):ti,ab,kw	578
8	(cranial NEAR/3 (xii OR xiis OR twelfth) NEAR/4 (stimulat* OR neurostimulat*)):ti,ab,kw	16
9	(tongue NEAR/4 neurostimulat*):ti,ab,kw	7
10	'electrostimulation'/exp	83430
11	(electric* NEAR/4 (stimulat* OR neurostimulat*)):ti,ab,kw	86950
12	electrotherap*:ti,ab,kw	2629
13	(electrostimulation NEAR/3 therap*):ti,ab,kw	198
14	(upper NEAR/4 airway NEAR/4 stimulat*):ti,ab,kw	444
15	('upper-airway' NEAR/4 stimulat*):ti,ab,kw	436
16	(sleep NEAR/4 therap* NEAR/4 system*):ti,ab,kw	67
17	'implantable neurostimulator'/exp	2668
18	(implant* NEAR/3 (stimulat* OR neurostimulat*)):ti,ab,kw	7173
19	inspire:ti,ab,kw	5504
20	aura6000:ti,ab,kw	6
21	imthera:ti,ab,kw	15
22	nyxoah:ti,ab,kw	3
23	(genio NEAR/3 (system* OR device)):ti,ab,kw	5
24	(hgns NEAR/2 system):ti,ab,kw	23
25	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	140140
26	#6 AND #25	938
27	osa:ti,ab,kw OR osas:ti,ab,kw OR oahs:ti,ab,kw OR osahs:ti,ab,kw	34756
28	#6 OR #27	86512
29	#25 AND #28	965

Database: Cochrane Library databases collection (Wiley) 1992 to present
Search date: 2020-01-22

#	Search	Hits
1	MeSH descriptor: [Sleep Apnea Syndromes] explode all trees	2296
2	MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees	1673
3	(sleep NEAR/4 (apnoea OR apnea OR hypopnea OR hypopnoea)):ti,ab,kw	6222
4	(sleep NEAR/4 disorder* NEAR/4 breath*):ti,ab,kw	2703
5	((sleep-disorder*) NEAR/4 breath*):ti,ab,kw	2619
6	(upper NEAR/4 airway NEAR/4 resistance NEAR/4 syndrome):ti,ab,kw	16
7	(OSA or OSAS or OAHS OR OSAHS):ti,ab,kw	3575
8	#1 OR #2 OR #4 OR #5 OR #6 OR #7	5531
9	((hypogloss* OR geniglosusu) NEAR/4 (stimulat* OR neurostimulat*)):ti,ab,kw	29
10	(cranial NEAR/3 (xii OR xiis OR twelfth) NEAR/4 (stimulat* OR neurostimulat*)):ti,ab,kw	1
11	(tongue NEAR/4 neurostimulat*):ti,ab,kw	2
12	MeSH descriptor: [Electric Stimulation] explode all trees	1916
13	MeSH descriptor: [Electric Stimulation Therapy] explode all trees	6630
14	(electric* NEAR/4 (stimulat* OR neurostimulat*)):ti,ab,kw	10215
15	electrotherap*:ti,ab,kw	693
16	(electrostimulation NEAR/3 therap*):ti,ab,kw	350
17	(upper NEAR/4 airway NEAR/4 stimulat*):ti,ab,kw	40
18	(upper-airway NEAR/4 stimulat*):ti,ab,kw	40
19	(sleep NEAR/4 therap* NEAR/4 system*):ti,ab,kw	87
20	MeSH descriptor: [Implantable Neurostimulators] explode all trees	182
21	(implant* NEAR/3 (stimulat* OR neurostimulat*)):ti,ab,kw	508
22	inspire:ti,ab,kw	299
23	aura6000:ti,ab,kw	2
24	imthera:ti,ab,kw	2

25	nyxoah:ti,ab,kw	0
26	(genio NEAR/3 (system* OR device)):ti,ab,kw	0
27	(hgns NEAR/2 system):ti,ab,kw	4
28	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	15352
29	#8 AND 28	857

DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1: Characteristics of the studies included – RCTs, direct comparison: intervention vs. comparator

Study reference/ID (NCT) Author year	Sites or regions, countries, time of study	Study type	Intervention [number of (randomized / enrolled) patients] Name device	Comparator(s) [number of (randomized / enrolled) patients] Name device	Patient population Clinical stage	Primary endpoint; patient-relevant secondary endpoints[a] Follow-up length
NCT01161420 Woodson et al 2014 [22] Industry-supported multicenter academic and clinical setting: Inspire Medical Systems	Belgium 1 site France 2 sites Germany 3 sites The Netherlands 1 site USA 15 sites 2010-2017 *10 Nov 2010 and 15 Feb 2012 (recruitment)*	Randomized controlled therapy withdrawal study	Upper airway stimulation (UAS) [23/46 patients] Inspire Medical Systems, Inc, Maple Grove, Minnesota	Until 13-month PSG was performed, then Upper airway stimulation OFF for 1 week (therapy withdrawal) (UAS) [23/46 patients] Inspire Medical Systems, Inc, Maple Grove, Minnesota	Moderate to severe obstructive sleep apnea (OSA) Intolerance or inadequate adherence to continuous positive airway pressure (CPAP) BMI>32 kg/m^2 excluded	Propensity for daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS). Daytime functioning, as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ). Intrusive snoring, as reported by participant and bed partner. Sleep-disordered breathing, as found in an overnight polysomnography (PSG). Follow-up: 13 and 18 months

AE: adverse event; N: number of randomized (included) patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus

Table A2: Characteristics of the studies included: non-RCTs, direct comparison: intervention vs. comparator

Study reference/ID (NCT) Author, year Funding	Sites or regions, countries, time of study	Study type	Intervention [number of patients enrolled] Name of device	Patient population Clinical stage	Primary endpoint; patient-relevant secondary endpoints[a] Follow-up length
NCT01186926 NCT01211444 Kezirian et al, 2014 [16]	Australia 4 sites USA 4 sites 2010-2013	Multicenter prospective single-arm open-label study	Upper airway stimulation (UAS) [31 patients] HGNS®; Apnex Medical, St Paul, MN, USA	Moderate to severe obstructive sleep apnea (OSA) Documented failure of positive airway pressure (PAP) BMI >40 kg/m^2 and previous surgery excluded	Primary: mean change in AHI and FOSQ total score (effectiveness); Freedom from serious adverse events (SAE) (Safety): Secondary (effectiveness): mean change for other polysomnographic and symptom measures Usage: proportion of nights with use and nightly hours of use Follow-up: implantation, 6 months and 12 months.
NCT01161420 Woodson et al 2018 [15] Industry-supported multicenter academic and clinical setting: Inspire Medical Systems	Belgium 1 site France 2 sites Germany 3 sites The Netherlands 1 site USA 15 sites 2010-2017 *10 Nov 2010 and 15 Feb 2012 (recruitment)*	Multicenter prospective single-arm open-label study	Upper airway stimulation (UAS) [126 patients] Inspire Medical Systems, Inc, Maple Grove, Minnesota	Moderate to severe obstructive sleep apnea (OSA) Intolerance or inadequate adherence to continuous positive airway pressure (CPAP) BMI>32 kg/m^2 excluded	Propensity for daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS). Daytime functioning, as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ). Intrusive snoring, as reported by participant and bed partner. Sleep-disordered breathing, as found in an overnight polysomnography (PSG). Follow-up: 12, 24, 36, 48 and 60 months
NCT03048604 Eastwood et al 2020 [18]	Australia 4 sites France 3 sites UK 1 site (not enrolment) April 2017 -February 2018	Multicenter prospective single-arm open-label study	Upper airway stimulation (UAS) [27 patients] Genio™ system (Nyxoah SA, Mont-Saint-Guibert, Belgium)	Moderate to severe obstructive sleep apnea (OSA) Intolerance or inadequate adherence to continuous positive airway pressure (CPAP) BMI>32 kg/m^2 excluded	Primary: Incidence of device-related serious advers events (safety); Change in the apnea-hypopnea index (AHI) (effectiveness) Secondary: Change in the 4% oxygen desaturation index (ODI) (effectiveness) Follow-up: 6 months
NCT02293746 Steffen et al 2019 [73]	Germany 3 sites July 2014 to December 2016	Phase IV, follow up-post market study,	Upper airway stimulation (UAS) [60 patients] Inspire Medical Systems, Inc, Maple Grove, Minnesota	Moderate to severe obstructive sleep apnea (OSA) Intolerance to positive airway pressure (PAP) BMI>35 kg/m^2 excluded	ESS, BMI, UAS usage download, AHI, ODI (effectiveness) Follow-up: 24, 36 months
NCT02293746 Hofauer et al 2019 [19]	Germany 2 sites July 2014 to December 2016	Phase IV, follow up-post market study,	Upper airway stimulation (UAS) [102 patients] Inspire Medical Systems, Inc, Maple Grove, Minnesota	Moderate to severe obstructive sleep apnea (OSA) Intolerance to positive airway pressure (PAP) BMI>35 kg/m^2 excluded	Objective and self-reported adherence to UAS (effectiveness) Follow-up: average 10.1 months before the study of adherence
NCT01796925 Friedman et al. 2016	7 centers: USA, Germany, Belgium	prospective, multicenter, single-arm feasibility study	Targeted hypoglossal neurostimulation (THN) [46 patients]	Exclusion criteria included ≥10% central sleep apnea,	Effectiveness primary efficacy endpoints assessed

Study reference/ID (NCT) Author, year Funding	Sites or regions, countries, time of study	Study type	Intervention [number of patients enrolled] Name of device	Patient population Clinical stage	Primary endpoint; patient-relevant secondary endpoints[a] Follow-up length
[20]	Between April and September 2013		ImThera aura6000™ system	clinically enlarged tonsils (3+ or 4+), Modified Mallampati IV,presence of nasal obstruction, syndromic craniofacial abnormalities, epiglottic obstruction, and evidence of positional OSA (as judged from baseline PSG as >50% reduction in AHI between supine and nonsupine positions). Individuals with other active implanted medical devices were also excluded.	changes in Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI) from baseline to 6 months postimplant using an overnight in-laboratory PSG. Secondary endpoints included changes in Arousal Index (ArI) and two surveys: the Epworth Sleepiness Scale (ESS) and the Sleep Apnea Quality of Life Index (SAQLI). Safety primary safety endpoints assessed serious adverse events (AEs), both short term (within 30 days postimplant) and long term (6 months postimplant). Short-term events occur <30 days since date of implant. Long-term events occur >30 days since date of implant. AHI responders were predefined as ≥50% decrease in AHI and AHI < 20. ODI responders were predefined as having a unanticipated adverse device events were observed. Follow-up: Baseline, 6 Months
NCT02907398 Thaler et al 2019 [21]	USA, Europe multicenter October 2016 to February 2019.	ADHERE Registry is a multicenter prospective observational study following outcomes of upper airway stimulation (UAS) therapyThe registry has enrolled 1,017 patients from October 2016 through February 2019.	Upper airway stimulation (UAS) [640, 6 months; 382, 12 months patients] Inspire Medical Systems, Inc, Maple Grove, Minnesota	Patients with moderate to severe OSA and those who could not or would not use CPAP as a primary therapy. AHI between 15 to 65 events per hour inclusive, who are intolerant to CPAP, and who are free of complete concentric collapse during sedated endoscopy	AHI, ESS (effectiveness) Following baseline and implant data collection, the registry collects information from two clinical visits during postimplantation follow-up: the post-titration visits, approximately 6 months post-implantation, and the final visit, approximately 12 months post-implantation. Adverse events (safety)

Table A3: Characterisation of the interventions – RCT / Non RCT, direct comparison: intervention vs. comparator

ID /Study	Intervention	Comparator	Time to titration
NCT01161420 Woodson et al 2014 [22]	Therapy Maintenance Group (ON) Stimulation cuff electrode on the distal branch of the right hypoglossal nerve. Pressure-sensing lead placed in the fourth or fifth right intercostal space, between the internal and external intercostal muscles, tunnelled to a subcutaneous implantable pulse generator. Device ON	Therapy Withdrawal Group (OFF) Same intervention but device was turned off for 1 week and remained off until the RCT PSG was performed	All participants had their device activated after a second baseline PSG 1 month following the implant procedure. Device parameters were adjusted for optimal therapy during titration PSG studies prior to the 12-month follow-up. No device adjustments were made during the 12-month, 18-month, or RCT PSG. Patient controls device with a remote (start, pause, and stop).
NCT01186926 NCT01211444 Kezirian et al, 2014 [16]	Implantable neurostimulator connected to a unilateral (generally right-sided) stimulation lead and two respiration subcutaneous sensing leads tunnelled to thorax.	No comparator	All participants had their device activated 1 month following the implant procedure (titration PSG). Patient controls device with a remote (start, pause, and stop). After allowing approximately 1 month following implantation for healing, each subject underwent a titration polysomnogram. Downloadable utilization data were stored in the devices. In-laboratory sleep studies were performed at 3, 6 and 12 months post implantation.
NCT03048604 Eastwood et al 2020 [18]	Stimulation delivered bilaterally and controlled from an externally worn unit that activates a small implanted battery-free submental stimulator at a predetermined, adjustable rate and duty cycle. One incision without leads/ tunnelling	No comparator	Device activated 4–6 weeks after implantation, titrated (optimised) at follow-up visits at 2, 3 and 4 months. External activation unit, attached to an adhesive disposable patch, placed under the chin by the participant prior to going to sleep. Removed by the participant in the morning, the disposable patch is discarded, and the activation unit recharged for its next use
NCT02293746 Steffen et al 2019 [73]	Stimulation cuff electrode on the distal branch of the right hypoglossal nerve. Pressure-sensing lead placed in the fourth or fifth right intercostal space, between the internal and external intercostal muscles, tunnelled to an subcutaneous implantable pulse generator.	No comparator	All participants had their device activated after a second baseline PSG 1 month following the implant procedure. At month 2 (M2) postimplantation, patients underwent PSG with UAS system optimization. 1- and 2-year follow-up assessments (M12 and M24) were also obtained. Patient controls device with a remote (start, pause, and stop).
NCT02293746 Hofauer et al 2019 [19]	Stimulation cuff electrode on the distal branch of the right hypoglossal nerve. Pressure-sensing lead placed in the fourth or fifth right intercostal space, between the internal and external intercostal muscles, tunnelled to an subcutaneous implantable pulse generator.	No comparator	All participants had their device activated after a second baseline PSG 1 month following the implant procedure The device was activated approximately 1 month after implantation. Further titrations were performed at months 2 and 3 post-implantation. Follow-up visits, which included home sleep polygraphies, were scheduled at month 6, 12, and from then on, every 12 months. Patient controls device with a remote (start, pause, and stop).
NCT01796925 Friedman et al 2016 [20]	The device was implanted unilaterally. The system consisted of two implanted components—an 11.5-cm3 IPG and a lead with six independent electrodes embedded in a silicone cuff—plus an external remote control. The cuff was	No comparator	Following a 3- to 4-week healing period, participants underwent in-laboratory PSG and titration of the device. 6 months follow-up

ID /Study	Intervention	Comparator	Time to titration
	placed around the HGN. The IPG was surgically implanted in an ipsilateral infraclavicular subcutaneous pocket		
NCT02907398 Thaler et al 2019 [21]	The cuff electrode is placed on the genioglossus branches of the hypoglossal nerve.	No comparator	Baseline, implantation visit, post-titration (6 months), and final visit (12 months). During the post-implantation visits, study investigators determine OSA severity by AHI via either an in-lab attended polysomnography or a type 3 home sleep apnea test, daytime sleepiness as reported by participants using the ESS, and objective therapy use of hours per night from data stored in the IPG.

Abbreviations: AHI: Apnea hypopnea index; ESS: Epworth Sleepiness Scale; HGN: Hypoglossal Nerve; IPG: Implanted Pulse Generator; OSA: Obstructive Sleep Apnea; PSG: Polysomnography; RCT: Randomized Control Trial.

Table A4: Baseline characteristics of the study populations – RCT / Non RCT, direct comparison: intervention vs. comparator

Study reference / ID Characteristics Category	Intervention	Comparator
NCT01161420 (Woodson et al_2014) [22]	**N[a]=23**	**N[a]=23**
Age [years], mean (SD)	57.1 ± 10.0	52.7 ± 10.4
Gender male %	95.6	82.6
BMI, kg/m2	28.4 ± 2.4	27.3 ± 2.4
Apnea hypopnea index (AHI) (SD)	31.3 ± 12.3	30.1 ± 11.4
Oxygen Desaturation index (ODI) (SD)	26.7 ± 13.0	26.8 ± 10.2
Percentage Sleep SaO2<90% (SD)	7.4 ± 8.3	5.6 ± 4.4
Functional Outcomes of Sleep Questionnaire (FOSQ) (SD)	15.1 ± 3.1	13.9 ± 2.6
Epworth Sleepiness Scale (ESS) (SD)	11.2 ± 5.3	11.3 ± 5.0
Neck size [cm] (SD)	41.6 ± 2.1	40.9 ± 3.6
Ethnicity	--	--
NCT01186926; NCT01211444 (Kezirian et al_2014) [16]	**31**	**--**
Age [years], mean (SD)	52.4 ± 9.4	--
Gender male %	65	--
BMI, kg/m^2 (SD)	32.4 ± 3.6	--
Apnea hypopnea index (AHI) (SD)	45.4 ± 17.5	--
Oxygen Desaturation index (ODI) (SD)	20.9 ± 17.3	--
Percentage Sleep SaO2<90%	--	--
Functional Outcomes of Sleep Questionnaire (FOSQ) (SD)	14.2 ± 2.0	--
Epworth Sleepiness Scale (ESS) (SD)	12.1 ± 4.6	--

Neck size [cm] Ethnicity (%)	- Non-Hispanic Caucasian (90)	- -
NCT01161420; (Woodson et al_2018) [15]	**126**	**--**
Age [years], mean (SD) Gender male % BMI, kg/m^2 Apnea hypopnea index (AHI) Oxygen Desaturation index (ODI) Percentage Sleep SaO2<90% Functional Outcomes of Sleep Questionnaire (FOSQ) Epworth Sleepiness Scale (ESS) Neck size [cm] Ethnicity	54.5 ± 10.2 83 28.4 ± 28.5 32.0 ± 11.8 28.9 ± 9.6 -- 14.3 ± 3.2 11.6 ± 5.0 - -	-- -- -- -- -- -- --
NCT03048604; (Eastwood et al_2020) [18]	**27**	
Age [years], mean (SD) Gender male % BMI, kg/m^2 Apnea hypopnea index (AHI) Oxygen Desaturation index (ODI) Percentage Sleep SaO2<90% Functional Outcomes of Sleep Questionnaire (FOSQ) Epworth Sleepiness Scale (ESS) Neck size [cm] Ethnicity (%)	55.9 ± 12.0 63 27.4 ± 3.0 23.7 ± 12.2 19.1 ± 11.2 5.0 ± 6.0 15.3 ± 3.3 11.0 ± 5.3 39.0 ± 4.2 (n=24) Caucasian (88.9) Hispanic (11.1)	-- -- -- -- -- -- -- -- -- --
NCT02293746; (Steffen et al_2019) [17]	**60**	**--**
Age [years], mean (SD) Gender male % BMI, kg/m2 Apnea hypopnea index (AHI) Oxygen Desaturation index (ODI) Percentage Sleep SaO2<90% Functional Outcomes of Sleep Questionnaire (FOSQ) Epworth Sleepiness Scale (ESS) Neck size [cm] Ethnicity	56.8 ± 9.1 97 28.8 ± 3.6 31.2 ± 13.2 28.5 ± 16.6 -- -- 12.4 ± 5.7 -- --	-- -- -- -- -- -- -- -- -- --
NCT02293746; (Hofauer et al_2019) [19]	**102**	**--**

Age [years], mean (SD) Gender male % BMI, kg/m2 Apnea hypopnea index (AHI) Oxygen Desaturation index (ODI) Percentage Sleep SaO2<90% Functional Outcomes of Sleep Questionnaire (FOSQ) Epworth Sleepiness Scale (ESS) Neck size [cm] Ethnicity (%)	56.7 ± 11.3 -- 29.4 ± 4.3 32.8 ± 13.9 27.6 ± 17.6 -- -- 12.9 ± 4.6 -- --	-- -- -- -- -- -- -- -- -- --
NCT01796925. Friedman et al. 2016 [20]	**46**	
Age [years], mean (SD) (range) Gender male % BMI, kg/m2 mean, range Apnea hypopnea index (AHI) Oxygen Desaturation index (ODI) Percentage Sleep SaO_2<90% Functional Outcomes of Sleep Questionnaire (FOSQ) Epworth Sleepiness Scale (ESS) Neck size [[cm]] Ethnicity	54.9 ± 11.1 (35.3-73.4) 94 (43/46) 30.8 ± 3.7 (20.2 – 36.9) -- -- -- -- -- --	-- -- -- -- -- -- -- -- -- --
NCT02907398 (Thaler et al 2019) [21]	**1,017**	
Age [years] (SD) Gender male (%), BMI, kg/m^2 Apnea hypopnea index (AHI), (interquartile range) Oxygen Desaturation index (ODI) Percentage Sleep SaO2<90% Functional Outcomes of Sleep Questionnaire (FOSQ) Epworth Sleepiness Scale (ESS), (SD) Neck size [cm] Ethnicity (%)	60 ± 11 74 29.3 ± 3.9 32.8 (23.6-45.0) -- -- -- 11.4±5.7 -- Caucasian (96)	-- -- -- -- -- -- -- -- -- --
Abbreviations: AHI: Apnea Hypopnea Index; a: Number of implanted patients; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; female; FOSQ: Functional Outcomes of Sleep Questionnaire; m: male; n: number of patients in the category; N: number of patients; ND: no data; ODI: Oxygen Desaturation index; RCT: randomized controlled trial; SD: standard deviation; vs.: versus		

Table A5: Results summary for safety outcomes

Study reference / ID ***(N patients)*** ***Device*** ***Follow-up***	**Serious adverse event (n events in n patients)**		**Non-serious adverse event (n events)***	
	Device-related	**Procedure-related**	**Device-related**	**Procedure-related**
NCT01186926 NCT01211444 Kezirian et al 2014 [16] *(N 31)* HGNS®; Apnex Medical *12 months of follow up*	- Device explantation due to lack of sufficient effectiveness (2 in 2 patients) - Device replacement due to dislodgement of stimulation lead cuff (2 in 2 patients)	- Device explantation due to infection (1 in 1 patient)	- Tongue abrasion (17)[ab]	- Numbness/pain at incision site (11)[ab]
NCT01161420 Woodson et al 2018 [15] Inspire Medical Systems, Inc *(N 124)* *12 months of follow-up*			- Discomfort due to electrical stimulation (81) - Tongue abrasion (28) - Dry mouth (10) - Mechanical pain associated with presence of the device (7) - Temporary internal device usability or functionality complaint (12) - Temporary external device usability or functionality complaint (11) - Mild infection device related (1) - Other acute symptoms (21)	- Postoperative discomfort related to incisions (47) - Postoperative discomfort independent of incisions (41) - Temporary tongue weakness (34) - Intubation effects (18) - Headache (8) - Other postoperative symptoms (22) - Mild infection (1)
NCT01161420 Woodson et al 2018 [15] Inspire Medical Systems, Inc *(N 97)* *5 years of follow-up*	Device replacement/reposition due to failures (9 in 8 patients)		- Discomfort due to electrical stimulation (61) - Tongue abrasion (21) - Dry mouth (10) - Mechanical pain associated with presence of the device (7) - Temporary internal device usability or functionality complaint (13) - Temporary external device usability or functionality complaint (34) - Other acute symptoms (18)	- Postoperative discomfort related to incisions (5) - Postoperative discomfort independent of incisions (1)

Study reference / ID *(N patients)* *Device* *Follow-up*	Serious adverse event (n events in n patients)		Non-serious adverse event (n events)*	
	Device-related	**Procedure-related**	**Device-related**	**Procedure-related**
NCT03048604 Eastwood et al 2020 [18] Genio ™ system *(N 27)* *6 months of follow-up*		-Device explantation due to infection (3 in 2 patients) -Impaired swallowing that led to a 1 day prolongation of hospitalization (1 in 1 patient)	- Local skin irritation due to the disposable patch (9) - Tongue abrasion (4) - Tongue fasciculation (4) - Discomfort due to electrical stimulation (3)	- Impairment or painful swallowing (8) - Dysarthia (7) - Haematoma (5) - Swelling or bruising around the incision site (5) - Abnormal scarring (5)
NCT02293746 Steffen et al 2019 [73] *(N 60) 24,* Inspire Medical Systems, Inc *36 months of follow-up*	- Sensing lead replacement due to insulation damage at the movable anchor (1 in 1 patient) - Sensing lead replacement (1 in 1 patient)		[c]	[c]
NCT02907398 Thaler et al 2019 [21] Inspire Medical Systems, Inc *(N 640)* *12 months of follow-up*	- Surgical intervention for device revision due to stimulation electrode dislodgement (1 in 1 patient) - Surgical intervention for stimulation electrode repositioning (2 in 2 patients)	- Infection without device explantation (2)	- Discomfort, device (15) - Stimulation-related discomfort (69) - Insomnia/arousal (27) - Tongue abrasion (26) - Device usability complaint related with activation (60)	- Infection without device explantation (2) Tongue weakness (3) - Swallowing or speech related (5) - Discomfort, incision/scar (22) - Other discomfort (20) - Postoperative, other[d] (20)
NCT01796925 Friedman et al 2016 [20] *(N 46)* aura6000™ system ImThera *6 months of follow-up*	- Surgical intervention with replacement of lead due to lack of sufficient effectiveness (1 in 1 patient) - Device migration (1 in 1 patient)	- Hematoma (1 in 1 patient) - Pain (3 in 3 patients). In 2 patients required replacement of the pulse generator - Bleeding (1 in 1 patient) - Other (5 in 4 patients) [e]	- Paresis (5) - Paresthesia (6)	- Anesthesia complication (1) - Hematoma (3) - Infection (4) - Pain (19) - Other (17) [e]

* One patient can have multiple events, at different points during follow-up
[a] Patients, not events
[b] Only the most frequent non-serious adverse event is reported in the article
[c] Information on non-serious adverse events was not found in the study
[d] Postoperative other includes shortness of breath, seroma, numbness of the throat, hoarseness during the day, and a mild tongue-base and epiglotic obstruction
[e] It was not possible to classify or specified the adverse events

List of planned, ongoing, withdrawn and completed studies without results

Table A6: List of planned, ongoing, withdrawn and completed studies without results with Hypoglossal Nerve Stimulations Systems

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT04031040 (EliSA)	October 2023	Interventional	110	Genio (TM) system therapy	No	Adult (≥ 18 years), All sex, with body Mass Index (BMI) < 35 kg/m2, AHI=15-65 events/hour by a PSG during the screening phase. Has either not tolerated, has failed o refused Positive Airway Pressure (PAP) or Mandibular Advancement Device (MAD) treatments	Incidence of all reported SAEs and all procedure- or device-related AEs Change in Apnea-Hypopnea Index from baseline Change in the quality of life measured by the Functional Outcomes of Sleep Questionnaire
NCT03868618 (DREAM)	June 2022	Interventional	136	Genio (TM) system	No	Adult (21 -75 years), all sex, BMI limitations, Likely suffer from moderate to severe OSA based on history and physical, Has either not tolerated, has failed o refused PAP, Willing and capable of providing informed consent	Incidence of device-related SAE Change in ODI (4%) Change in the FOSQ10
NCT03844295 (AIRSTIM)	March 2020	Interventional (Monocentric, prospective, controlled, patient single-blind study)	6	Inspire® Upper Airway Stimulation System	Inactivated Inspire® Upper Airway Stimulation System	Adult (18 -80 years), all sex, Patient with moderate to severe OSA based on an established diagnosis of OSA (15≤AHI<65) by polysomnography or respiratory polygraphy not older than three years. Patient with moderate to severe OSA naïve of treatment or with difficulty accepting or adhering to PAP treatment. Willing and capable to have stimulation hardware permanently implanted, and to use the patient programmer to activate the stimulation Willing and capable to return for all follow-up visits and conduct	Short-term efficacy of a new treatment for OSA on systolic blood pressure variability during sleep

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						sleep studies at home, including the evaluation procedures and filling out questionnaires Willing and capable of providing written informed consent	
NCT03763682 (BETTER SLEEP)	January 2020	Interventional (prospective, open-label, 2 groups)	40	Genio (TM) bilateral hypoglossal nerve stimulation system	No	Adult (21 -75 years), all sex, BMI ≤ 32 kg/m2, AHI of 15-50 events/hour. Participants who have either not tolerated, have failed or refused PAP treatments.	Incidence of serious device-related adverse events recorded during the study Change from baseline to 6 months post implantation in the AHI (time frame: 6 month) Change from baseline to 6 months post implantation in Oxygen Desaturation Index (ODI) (time frame: 6 month)
NCT03760328 (EFFECT)	June 2020	Interventional (multi-center, randomized, crossover study)	100	Inspire® Upper Airway Stimulation System	Active Comparator: therapeutic stimulation (optimal therapy setting for home use) Sham Stimulation (Control Group): stimulation voltage programmed at 0.1 volts	Adult (≥ 18 years), all sex and have been implanted and using the Inspire Therapy for at least six months. Willing and capable to undergo three in-lab PSGs in a one-month timeframe. Willing and capable of having reduced Inspire stimulation for one week. Willing and capable of providing informed consent	Change in AHI from Baseline to Visit 1 and Visit 2 (Time Frame: Baseline through Visit 1 (1 week) and Visit 2 (2 weeks)) Change in ESS from Baseline to Visit 1 and Visit 2 (Time Frame: Baseline through Visit 1 (1 week) and Visit 2 (2 weeks))
NCT02413970	December 2021	Interventional (single-arm study)	127	Inspire® Upper Airway Stimulation System	No	Adult (≥ 22 years), all sex, Likely suffer moderate-to-severe OSA based on history and physical or have an established diagnosis of OSA (AHI >= 15) based on a prior sleep study. Documentation the subject not effectively treated with PAP therapy. Willing and capable to have stimulation hardware permanently implanted, and	Long-term Device-Related SAEs (Time Frame: 5 Years Post-Implant) Therapy Specific AEs (Time Frame: 5 Years Post-Implant) Long-term Therapy-Related AEs (Time Frame: 5 Years Post-Implant)

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						to use the patient remote to activate the stimulation. Willing and capable to return for all follow-up visits and conduct sleep studies at home, including the evaluation procedures and filling out questionnaires. Willing and capable of providing informed consent	

Abbreviations: AE: Adverse Events; AHI: Apnea Hypopnea Index; ESS: Epworth Sleepiness Scale; FOSQ10: Functional Outcomes of Sleepiness questionnaire; MAD: Mandibular Advancement Device; ODI: Oxygen Desaturation Index; PAP: Positive Airway Pressure; SAE: Serious Adverse Events.

Sources: ClinicalTrials.gov

Risk of bias tables

Table A7: Risk of bias – study level (RCTs)

Trial	Adequate generation of randomization sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – study level
			Patient	Treating person			
Woodson 2014 [22]	Unclear[a]	Unclear[a]	No[b]	No[b]	Yes	No[c]	High risk
Footnotes: Yes / No / Unclear/ Low Risk / High Risk							

Abbreviations: OSA (Obstructive Sleep Apnea); UAS (Upper Airway Stimulation)

a: The only information about randomization methods is a statement that the study was randomized
b: lack of subject or investigator blinding. As the participants experience a physical forward movement of their tongue during therapy, blinding of the participants is not feasible. Investigators were not blinded due to their roles in therapy administration.
c: Intention To Treat principle not stated; evidence not applicable to the population of interest since participants were only those who respond positively to the therapy in the previous year
Sources: [22]

Table A8: Risk of bias – outcome level (RCTs)

Endpoint Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
AHI change after one week with therapy ON or OFF						
Woodson 2014 [22]	H	N[a]	U[b]	Y	N[c]	H[d]
ODI change after one week with therapy ON or OFF						
Woodson 2014 [22]	H	N[a]	U[b]	Y	N[c]	H[d]
HT change after one week with therapy ON or OFF						
Woodson 2014 [22]	H	N[a]	U[b]	Y	N[c]	H[d]
FOSQ change after one week with therapy ON or OFF						
Woodson 2014 [22]	H	N[a]	U[b]	Y	N[c]	H[d]
ESS change after one week with therapy ON or OFF						
Woodson 2014 [22]	H	N[a]	U[b]	Y	N[c]	H[d]
Footnotes: Yes / No / Unclear/ Low Risk / High Risk						

Abbreviations: OSA (Obstructive Sleep Apnea); UAS (Upper Airway Stimulation)

a: lack of subject or investigator blinding. As the participants experience a physical forward movement of their tongue during therapy, blinding of the participants is not feasible. Investigators were not blinded due to their roles in therapy administration.
b: Intention To Treat principle not stated.
c: information about randomization methods is not stated; evidence not applicable to the population of interest since participants were only those who respond positively to the therapy in the previous year
d: High risk of bias on study level.
Sources: [22]

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Table A9: **Risk of bias – study-level of non-randomised studies: IHE Quality Appraisal Checklist for Case Series Studies**

Study	19 criteria checklist: critical appraisal single-group studies									
	1. Was the hypothesis/aim/objective of the study clearly stated?	2. Was the study conducted prospectively?	3. Were the cases collected in more than one centre?	4. Were patients recruited consecutively?	5. Were the characteristics of the patients included in the study described?	6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	7. Did patients enter the study at a similar point in the disease?	8. Was the intervention of interest clearly described?	9. Were additional interventions (co-interventions) clearly described?	10. Were relevant outcome measures established a priori?
Woodson_2018 (STAR) [15]	YES	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	YES
Thaler_2019 (ADHERE) [21]	YES	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	YES
Friedman_2016 (THN2) [20]	YES	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	YES
Kezirian_2014 (APNEX) [16]	YES	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	YES
Hofauer_2019 (GPM) [19]	YES	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	YES
Steffen_2019 (GPM) [73]	YES	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	YES
Eastwood_2020 (BLAST OSA) [18]	YES	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	YES

Study	19/ criteria checklist: critical appraisal single-group studies									
	11. Were the relevant outcomes measured using appropriate objective/subjective methods?	12. Were the relevant outcome measures made before and after the intervention?	13. Were the statistical tests used to assess the relevant outcomes appropriate?	14. Was follow-up long enough for important events and outcomes to occur?	15. Were losses to follow-up reported?	16. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	17. Were the adverse events reported?	18. Were the conclusions of the study supported by the results?	19. Were both competing interests and sources of support for the study reported?	TOTAL AFFIRMATIVE
Woodson_2018 (STAR) [15]	YES	YES	YES	YES	YES	YES	YES	YES	YES	18/19
Thaler_2019 (ADHERE) [21]	YES	YES	YES	YES	NO	YES	YES	YES	YES	18/19
Friedman_2016 (THN2) [20]	YES	YES	YES	PARTIAL	YES	YES	YES	YES	PARTIAL	16/19
Kezirian_2014 (APNEX) [16]	YES	YES	YES	YES	YES	YES	YES	YES	YES	18/19
Hofauer_2019 (GPM) [19]	YES	YES	YES	YES	PARTIAL	YES	NO	YES	PARTIAL	15/19
Steffen_2019 (GPM) [73]	YES	YES	YES	YES	YES	YES	PARTIAL	YES	PARTIAL	16/19
Eastwood_2020 (BLAST OSA) [18]	YES	YES	YES	PARTIAL	YES	YES	YES	YES	YES	17/19

Table A10: EFFECTIVENESS GRADE assessment table

Question: Is HGNS more effective than no treatment?

Bibliography: Woodson 2014 [22]

Certainty assessment							No patients		Effect		Certainty	Importance
No of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HGNS ON**	**HGNS OFF**	**Absolute Change after a week (mean ± SE)**	**Relative Difference of change ON – OFF (95% CI)**		
AHI change after one week with therapy ON or OFF (assessed with PSG) [a]												
1	Randomised trial	serious [b]	serious [c]	very serious [d]	very serious[c,e]	none	23	23	ON: 1.7 ± 6.4 OFF: 18.2 ± 15.6	16.4 (9.2- 23.7) P value < .001	⊕◯◯◯ VERY LOW	CRITICAL
ODI change after one week with therapy ON or OFF (assessed with PSG) a												
1	Randomised trial	serious [b]	serious [c]	very serious [d]	very serious[c,e]	none	23	23	ON: 1.6 ± 5.8 OFF: 17.0 ± 14.5	15.4 (8.7- 22.1) P value <.001	⊕◯◯◯ VERY LOW	CRITICAL
HT change after one week with therapy ON or OFF (assessed with PSG) a												
1	Randomised trial	serious [b]	serious [c]	very serious [d]	very serious[c,e]	none	23	23	ON: -1.0 ± 6.4 OFF: -6.5 ± 10.8	5.4 (0.1, 10.7) P value .04	⊕◯◯◯ VERY LOW	CRITICAL
FOSQ change after one week with therapy ON or OFF (assessed with FOSQ score) [a,f]												
1	Randomised trial	serious [b]	serious [c]	very serious [d]	very serious[c,e]	none	23	23	ON: 0.0 ± 1.0 OFF: -2.3 ± 3.0	-2.3 (-3.8, -0.9) P value .001	⊕◯◯◯ VERY LOW	CRITICAL
ESS change after one week with therapy ON or OFF (assessed with ESS score) [a,g]												
1	Randomised trial	serious [b]	serious [c]	very serious [d]	very serious[c,e]	none	23	23	ON: -0.3 ± 1.8 OFF: 3.8 ± 4.6	4.2 (2.0, 6.4) P value < .001	⊕◯◯◯ VERY LOW	CRITICAL

Abbreviations: AHI: Apnea Hypopnea Index; CI: Confidence Interval; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; HGNS: Hypoglossal Nerve Stimulation; HT: Hypoxemia Time (percentage total sleep time with oxygen saturation < 90%); ODI: Oxygen Desaturation Index; UAS: Upper Airway Stimulation; PSG: Polysomnogram.

a: Intervention with therapy either "ON" or "OFF" was performed during the 13-month window (RCT study) and then therapy was resumed. The OFF group had the device turned off for 1 week and remained off until the RCT PSG was performed. The ON group continued nightly use of the device and therapy remained on until and during the RCT PSG. Changes in AHI, ODI, hypoxemia time (percentage total sleep time with oxygen saturation <90%), FOSQ and ESS between the 12-month and RCT PSG were calculated. A paired *t* test was used to evaluate change differences between groups.

b: Randomization is not explained. Lack of subject and investigator blinding. Type of analysis (i.e.: Intention to treat) is not stated.

c: Evidence from only one and small study.

d: Surrogate outcome; in addition, only responders were included in the study, so the population is not representative of the population of interest

e: A wide confidence interval (CI) around the estimate of the effect.

f: Normal FOSQ is a score greater than 17.9.

g: Normal ESS is a score of 10 or less.

Table A11: SAFETY GRADE assessment tables

SERIOUS ADVERSE EVENTS

Question: Is HGNS safe? **Serious** adverse events

Bibliography: Eastwood et al [18]; Friedman et al [20]; Kezirian et al [16]; Steffen et al [17]; Thaler et al [21]; Woodson et al [15]

Certainty assessment							No patients		Effect		Certainty	Importance
No of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HGNS**	**Control**	**Relative**	**Absolute. N of events (events per patient)**		
Serious device-related adverse events in the first year of follow up*												
5	observational studies [a]	serious [b]	serious [c]	not serious	not serious	none	868	-	-	9 (0.01)	⨁◯◯◯ VERY LOW	CRITICAL
Serious procedure related adverse events in the first year of follow up*												
5	observational studies [a]	serious [b]	serious [c]	not serious	not serious	none	868	-	-	15 (0.02)	⨁◯◯◯ VERY LOW	CRITICAL
Serious device-related adverse events in subsequent years of follow-up (follow up: range >12 months to 60 months)*												
2	observational studies [a]	serious [b]	not serious	not serious	not serious	none	157	-	-	11 (0.07)	⨁◯◯◯ VERY LOW	CRITICAL

Abbreviations: HGNS: Hypoglossal Nerve Stimulation.
*: A patient can declare more than one event, more than one time, in each visit
a: Prospective single-arm to follow outcomes.
b: No control group. Follow-up mid-term. Conflict of interest & funding: some authors related to the MAH. See Table Ax IHE Quality Appraisal Checklist for Case Series Studies.
c: There is inconsistency on proportion of events reported among studies. The largest study has a lower proportion compared with the other studies.

NON-SERIOUS ADVERSE EVENTS
Question: Is HGNS safe? **Non-serious** adverse events
Bibliography: Eastwood et al [18]; Friedman et al [20]; Kezirian et al [16]; Steffen et al [17]; Thaler et al [21]; Woodson et al [15]

Certainty assessment							No patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HGNS	Control	Relative	Absolute. N of events (events per patient)		
Non-serious device-related adverse events in the first year of follow-up*												
5	observational studies [a]	serious [b]	serious [c]	not serious	not serious	none	868	-	-	416 (0.48)	⊕◯◯◯ VERY LOW	CRITICAL
Non-serious procedure related adverse events in the first year of follow up*												
5	observational studies [a]	serious [b]	serious [c]	not serious	not serious	none	868	-	-	328 (0.38)	⊕◯◯◯ VERY LOW	IMPORTANT
Non-serious device-related adverse events in subsequent years of follow-up (follow up: range >12 months to 60 months)*												
2	observational studies [a]	serious [b]	not serious	not serious	not serious	none	157	-	-	164 (1.04)	⊕◯◯◯ VERY LOW	CRITICAL
Non-serious procedure related adverse events in subsequent years of follow-up (follow up: range >12 months to 60 months)*												
2	observational studies [a]	serious [b]	not serious	not serious	not serious	none	157	-	-	6 (0.04)	⊕◯◯◯ VERY LOW	IMPORTANT

HGNS: Hypoglossal Nerve Stimulation;
*: A patient can declare more than one event, more than one time, in each visit
a: Prospective single-arm to follow outcomes.
b: No control group. Follow-up mid-term. Conflict of interest & funding: some authors related to the MAH. See Table Ax IHE Quality Appraisal Checklist for Case Series Studies.
c: There is inconsistency on proportion of events reported among studies. The largest study has a lower proportion compared with the other studies.

Applicability tables

Table A12: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population for this assessment were adult patients with moderate to severe Obstructive Sleep Apnea (OSA) who present inadequate adherence or failure to a positive airway pressure (PAP) systems or to other non-invasive procedures. The RCT included patients with severe obstructive sleep apnea (OSA), intolerance or inadequate adherence to continuous positive airway pressure (CPAP) with a AHI mean of 31.3 ± 12.3 for intervention group and 30.1 ± 11 for comparator group. The age mean was 57.1 ± 10.0 for intervention group and 52.7 ± 10.4 years for comparator group. The BMI was 28.4 ± 2.4 for intervention group and 27.3 ± 2.4 for comparator group. The study presents the limitation that the intervention was only applied to the 36.51% of the patients that responded positively to the responders of the UAS therapy In non RCT studies, the included patients with moderate or severe OSA, intolerance or inadequate adherence to CPAP, with a range of AHI between to 23.4 to 45.4. The age range 52.4-60 and BMI range 27.4-32.4.
Intervention	The devices of the studies included in this assessment were: Genio TM system, Inspire®, ImThera aura6000™ system. These devices have different implantation procedures. Genio™ does not have a stimulation generator located in the thorax, so any adverse event related to this site of intervention would be overestimated in the analysis.
Comparators	Only one is a comparative study. The comparator was device turned off that matches with comparator of PICO. In the intervention arm the device was left running and was switched off in the comparator arm for 1 week.
Outcomes	All critical outcomes with the exception of overall mortality and cardiovascular events were reported in the evidence retrieved. No information regarding cerebrovascular events was reported

Abbreviations: AHI: Apnea Hypopnea Index; BMI: Body Mass Index. CPAP: Continuous Positive Airway Pressure, HT: Hypoxemia Time (percentage total sleep time with oxygen saturation < 90%). ODI: Oxygen Desaturation Index; OSA: Obstructive Sleep Apnea; PAP: Positive Airway Pressure.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A13: Regulatory status

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
Inspire® UAS, model 3024 + model 3028	EU	CCE	YES	Inspire UAS is used to treat a subset of patients with moderate to severe OSA (apnea-hypopnea index [AHI] of greater than or equal to 20 and less than or equal to 65). Inspire UAS is used in adult patients 22 years of age and older who have been confirmed to fail* or cannot tolerate positive airway pressure (PAP) treatments (such as continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP] machines) and who do not have a complete concentric collapse at the soft palate level. UAS is also intended as an alternative to uvulopalatopharyngoplasty or sphincter expansion pharyngoplasty.	-Patients with complete concentric collapse of the soft palate or any anatomical finding (e.g., malformations for surgical resections) that would compromise the performance of upper airway stimulation -Patients who have severely compromised neurological control of the upper airway (e.g., intrinsic neuromuscular disease or other neurologic deficits -Patients who are pregnant or plan to become pregnant. Hypoglossal Nerve Stimulation therapy has not been evaluated for safety or efficacy during pregnancy -Previous surgery within 3 months on the soft-palate tissue -Hypersensitivity to a tissue contacting material -Patients who require magnetic resonance imaging (MRI) other than what is specified in the MR Conditional labeling* [3] * for Model 3028, patients with an MR Conditional system can undergo an MRI scan.	October 2010, renewed in 13/06/2019 Expiry date: 19/10/2020 [4]	Yes	CE 562872
Inspire® UAS, model 3024 + model 3028	USA	FDA	YES			April 2014, renewed in May 2017 [23]	Yes	P130008 & P130008-S016
Upper airway stimulation (UAS)	Australia New Zealand	Health PACT	Investigational stage			March 2015 licence	Yes	WP097 (licence no.)
aura6000™ System	EU	CCE	YES	The *aura6000*™ System is indicated for use in patients who cannot or will not tolerate positive airway pressure (PAP) therapy for the treatment of obstructive sleep apnea.	-Central sleep apnea -The safety and effectiveness of this neurostimulation system has not been established for pediatric use. Warnnings: -Magnetic Resonance Imaging (MRI)—Implanted patients should not be subjected to MRI. MRI exposure may result in dislodgement of implanted com-	2012 Renewed in March 2016 and March 2018; Expiry date: 1st March 2023 [15]	Yes	3807429CN
aura6000™ System	USA	FDA	YES			In 2014 FDA approved IDE	Yes	NCT02263859

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
					ponents, heating of the IPG, lead and/or electrode(s) which may in turn cause tissue damage, damage to the device electronics, and/or voltage induction through the lead and IPG. Implant Damage—Severe burns may result if the IPG case is pierced and tissue is exposed to battery chemicals. Never implant a damaged IPG. Interaction with Cardiac Devices—When a patient's medical condition requires both this device and an implanted cardiac device (e.g. pacemaker, defibrillator), clinicians involved with both devices should discuss the possible interactions between the devices before surgery. Interactions could include: • Defibrillation therapy from an implanted defibrillator may damage the neurostimulator. • The cardiac device may sense the neurostimulator pulses and respond inappropriately.			
Nyxoha's Genio® system	EU	CCE	YES	Nyxoah Genio™ System is intended to be used as second line therapy for people with moderate to severe OSA who are not compliant or have refused continuous positive airway pressure (CPAP) therapy [13].	NF	March 2012	Yes	-
Nyxoah Genio™ System	UK						expected to be launched into the UK NHS	-

Abbreviations: IDE = investigational device exemption; HealthPACT = Health Policy Advisory Committee on Technology. *PAP failure is defined as an inability to eliminate OSA (AHI of greater than 20 despite PAP usage), and PAP intolerance is defined as: (1) Inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night), or (2) Unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it). ** two supplement approved FDA (P13008/S016 for Model 3028 IPG; P13008/S021 to expand the Apnea Hypopnea Index (AHI) range from 20 to 65 events per hour to 15 to 65 events per hour).
Sources: user manuals/technical documents

Table A14: Summary of (reimbursement) recommendations in European countries for the technology

Country and issuing organisation	Status of reimbursement of HGNS	Recommendations and restrictions on HGNS following assessments
Austria[1] /LBI-HTA	Not reimbursed.	The technology has been assessed twice. The inclusion in the Austrian catalogue of benefits is currently not recommended based on the available evidence. A new evaluation is proposed for the year 2021 [63].
Croatia[1]	Not reimbursed.	Not assessed.
UK1 /NICE	Not reimbursed, if used special arrangements.	Current evidence on the safety and efficacy of hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research [23].
Germany[1] [29]	The technology is reimbursed with an add-on remuneration (about 20.000 €) in the in-hospital sector, not reimbursed in the out-of-hospital sector.	The technology has not been assessed (partly implantable stimulation systems currently scrutinized for assessment).
Italy[1]	Not reimbursed.	Not assessed.
Lithuania[1]	Not reimbursed.	Not assessed.
Poland[1]	Not reimbursed.	Not assessed.
Romania[1]	Not reimbursed.	Not assessed.
Sweden [31,75]	No details available regarding the current reimbursement status. According to the 2015 HTA report the technology was expected to be introduced in the Nordic countries during the spring 2015. The recommendations were to restrict its use to a limited number of centres in Sweden.	The 2015 HTA report assessing the evidence for hypoglossal nerve stimulation therapy in patients with obstructive sleep apnoea refractory to continuous positive airway pressure shows that “the therapy may substantially reduce important measures of OSA severity. Patient selection appears to be essential to the success of therapy. Severe device-related adverse events are rare. The hypoglossal nerve stimulation treatment is expensive and further studies with long-term follow-up are needed.”
Switzerland [29]	Reimbursed through generic Neurostimulation DRG (Diagnosis Related Group).	No details are available about the assessment and status of recommendation.
Belgium [29]	Not reimbursed.	No details are available about the assessment and status of recommendation.
The Netherlands[29]	Reimbursed through specific DRG.	No details are available about the assessment and status of recommendation.
France [29]	Not reimbursed.	No details are available about the assessment and status of recommendation.
Spain	Not reimbursed; nor included in the National Health System catalogue of benefits	The decision on coverage and provision in the National Health System will be evaluated once the ongoing assessment is available

Country and issuing organisation	Status of reimbursement of HGNS	Recommendations and restrictions on HGNS following assessments
For countries with indication specific reimbursement include only the recommendations for the indication under assessment **Include a reference to any publically available guidance document**		

Abbreviations: DRG: diagnosis-related group; NI: No information; NUB: New Diagnostic and Treatment Methods; OSA: Obstructive Sleep Apnea.
Sources: 1 EUnetHTA partners from the respective countries provided the information. [31]

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1	**Ethical**	
1.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
	We could not find specific evidence to reply appropriately to this question. However, the introduction of this new technology could imply ethical issues if an equitative access is not warranted. In order to avoid equity barriers, more studies to define the population who can benefit most of the use of the technology are required.	
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2	**Organisational**	
2.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	No
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
	Although no specific literature has been found to appropriately compare this new technology with the standard of care in terms of organizational issues, it is reasonable to assume there might exist implementation issues related to learning curves and requisite skills for conducting HGNS. The implementation of this technology will require specific training not only for health care professionals but also for patients.	
3	**Social**	
3.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4	**Legal**	
4.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No