EUnetHTA Joint Action 3 2016-2020

Hypoglossal nerve stimulation systems for treatment of obstructive sleep apnoea

Project ID: ***OTCA21***

Project description and planning

Agencia de Evaluación de Tecnologías Sanitarias-Instituto de Salud Carlos III

National School of Public Health, Management and Professional Development

This report is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

Version Log

Version number	Date	Modification	Reason for the modification
V1	12/12/2019	Preliminary version	Comments from DR, co-authors
V2	13/01/2020	First Draft	Scoping meeting
V3	21/01/2020	Second Draft	Inclusion of suggestions of Co-Authors, External Experts and Manufacturers (Fact-check)

CONTENTS

List of tables

1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Agencia de Evaluación de Tecnologías Sanitarias-Instituto de Salud Carlos III AETS -ISCIII	Author	Spain	Develop first draft of EUnetHTA project plan, amend the draft if necessary. Perform the literature search Carry out the assessment: answer assessment elements (Production of EFF and SAF domains), fill in checklist regarding potential "ethical, organisational, patient and social and legal aspects" of the HTA Core Model® for rapid REA Support the production of all domains and quality check the steps of their production (data, information, sources) Send "draft versions" to reviewers, compile feedback from reviewers and perform changes according to reviewers comments Prepare final assessment and write a final summary of the assessment
2.	National School of Public Health, Management and Professional Development NSPHMPD	Co-Author	Romania	Review the project plan draft. Carry out the assessment: answer assessment elements (Production of CUR and TEC domains) Support the production of all domains and quality check the steps of their production (data, information, sources). Contribute to answering questions related to potential ethical, organisational, patient, social, and legal aspects if needed. Approve/endorse conclusions drawn as well as all draft versions and the final assessment including the executive summary.
3.	National Institute of Public Health NIPHB	Dedicated Reviewer	Romania	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. •Review methods, results, and conclusions based on the original studies included.

				•Provide constructive comments in all the project phases
4.	Swiss Network for Health Technology Assessment SNHTA	Dedicated Reviewer	Switzerland	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. •Review methods, results, and conclusions based on the original studies included. •Provide constructive comments in all the project phases
5.	Servicio de Evaluación del Servicio Canario de la Salud – Fundación Canaria Instituto de Investigación Sanitaria de Canarias (SESCS-FISC)	Dedicated Reviewer	Spain	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts. •Review methods, results, and conclusions based on the original studies included. •Provide constructive comments in all the project phases
Contributors				
6.	Dra. Marina Carrasco ENT, University Hospital, Valencia, Spain	External expert	Spain	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original studies included; •Provide constructive comments in all the project phases
7.	Dra. Irene Cano Pneumologist, Respiratory Sleep Unit. Madrid, Spain	External expert	Spain	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original studies included; •Provide constructive comments in all the project phases
8.	TBD	Medical Editor		
9.	Agencia de Evaluación de Tecnologías Sanitarias-Instituto de Salud Carlos III AETS-ISCIII	Project Manager	Spain	Project management

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
INSPIRE Medical System (USA)	Manufacturer-fact check of project plan, 2nd draft assessment; submission template
LivaNova PLC London	Manufacturer-fact check of project plan, 2nd draft assessment; submission template
NYXOAH (Belgium)	Manufacturer-fact check of project plan, 2nd draft assessment; submission template
Patient/consumer representative groups	Individual patients

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**06/06/2019**	**15/05/2020**
Scoping phase	06/06/2019	22/01/2020
Identification of manufacturers, external experts, manufacturers and patients	06/06/2019	15/10/2019
Scoping, development of draft Project Plan	02/12/2019	22/01/2020
Consultation of draft Project Plan with dedicated reviewers, clinical experts, patients and manufacturers	12/12/2019	17/01/2020
Internal Scoping e-meeting with authors, dedicated reviewers and clinical experts	08/01/2020	13/01/2020
Amendment of draft Project Plan & final Project Plan available	14/01/2020	17/01/2020
Assessment phase	20/01/2020	15/05/2020
Writing first draft rapid assessment	20/01/2020	27/02/2020
Review by dedicated reviewer(s)	28/02/2020	06/03/2020
Writing second draft rapid assessment	09/03/2020	18/03/2020
Review by external clinical experts and fact check by manufacturers	19/03/2020	27/03/2020
Writing third draft rapid assessment	30/03/2020	06/04/2020
Medical editing	07/04/2020	16/04/2020
Writing of final version of rapid assessment	17/04/2020	22/04/2020
Formatting	23/04/2020	28/04/2020
Final version of REA		[week from 27/04/ to 30/04/2020]

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on other technologies. In addition, the aim is to apply those collaboratively produced assessments in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies	Production of 1 (rapid) relative effectiveness assessment for the use of Hypoglossal Nerve Stimulation (HGNS) in adult patients with moderate to severe obstructive sleep apnoea (OSA) who present inadequate adherence to a positive airway pressure systems or to other non-invasive procedures.
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.

This rapid assessment addresses the research question whether the use of Hypoglossal Nerve Stimulation (HGNS) is effective and safe in adult patients with moderate to severe obstructive sleep apnoea (OSA) who present inadequate adherence to a positive airway pressure systems or to other non-invasive procedures, compared to no treatment.

This topic is of relevance for the Spanish common services portfolio of the National Health System. The HGNS has been requested to be included and further reimbursed in the Spanish common services portfolio.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
The HTA Core Model Application for rapid Relative Effectiveness Assessment (REA) (4.2) will be the primary source for selecting assessment elements. The selected assessment element generic questions will be translated into research questions. For “Description and technical characteristics of technology” (TEC) and “Health problem and current use of technology” (CUR) domains a descriptive analysis will be performed, based on information from different sources: • Input from manufacturers, particularly related to questions on CE mark, marketing, availability and current use. The Medical Devices Evidence Submission template will be sent to all relevant manufacturers of the technology under assessment. Manufacturers will be asked to submit non-confidential documents, focusing on the technical characteristics and current use of the technology and on unpublished trial results.

- Input from clinical experts, particularly related to description of disease, current treatment, current use and best available epidemiological data. The clinical experts will be asked to verify the relevance and accuracy of the information and citations.
- Clinical guidelines: A search for current clinical guidelines in the Guidelines International database (G-I-N) will be performed by the author.
- Relevant literature identified by the literature search for the EFF and SAF domains.

A quality assessment would be conducted depending on the type of studies or information sources included in these two domains.

For Effectiveness (EFF) and Safety (SAF) domains, we will perform a systematic literature search. Two authors will independently screen the titles and abstracts and select studies according to the pre-defined inclusion and exclusion criteria. The full-text publications will be retrieved by the author, and the full-text examination will be performed by two authors independently. The authors will provide a list of included and excluded studies. Discrepancies will be resolved by discussion or with the help of a third party.

The Risk of bias (RoB) assessment of the included studies will be done according to the Cochrane Risk of bias tool on study and outcome level [1]. The 'Risk of bias' of each included trial will be assessed by two authors independently. Any disagreements will be resolved by consensus or by consulting a third party. The strength of evidence for all critical outcomes will be rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of evidence [2]. The results of the rating will be presented in GRADE Summary of Findings (SoF) tables.

Table 2-3: Planned literature search strategy

Literature search strategy
For EFF and SAF domains a systematic literature search will be performed using the bibliographic databases PubMed, MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials and Cochrane Database for Systematic Reviews, according to the predefined search strategy. A search in the clinical trials registries ClinicalTrials.gov, EU Clinical Trials Register and International Clinical Trials Registry Platform (ICTRP) will be carried out for ongoing studies. In addition to the electronic search, a hand search (in reference lists of relevant studies), as well as an internet search, including guidelines databases GIN, and HTA agencies websites, will be performed. A search of regulatory documents will be carried out in US Food and Drugs Administration. For the identification of studies, different search strategies adapted to each database will be designed, combining with controlled terms (MeSH and EMTREE) and free text for indications (Sleep Apnea, Obstructive Sleep Apnea, Upper Airway Resistance Syndrome) and intervention (Upper Airway Stimulation, Implantable Neurostimulators, Electric Stimulation Therapy, Hypoglossal Nerve Stimulation, Cranial Nerve XII). Inclusion criteria: human subjects, without language restriction and according to PICO criteria. Exclusion criteria: Studies that do not fulfil the PICO question will be excluded.

In order to avoid possible patient overlap in the studies, if the same institution has published sequential studies, the study with the largest number of cases will be chosen, strengthen the assessment elements for the identification and exclusion of duplicate publications. All titles and abstracts retrieved by electronic searching will be downloaded to a reference manager (EndNote X8), and duplicates will be removed.

Table 2-4: Plan for data extraction

Planned data extraction
Data to be extracted from the studies included: • Information about the study (authors, year of publication, setting/country, study design, clinical trial identification number/ registry identifier and funding source). • Participant/patient characteristics (diagnosis, number of participants in each arm, age, clinical stage, any relevant risk category or risk factor). • Intervention and control characteristics (description of procedure, comparator, name/type of the device, frequency of intervention per patient, length of follow up and loss to follow up). • Outcomes (see section 2.2.2). For missing data trial authors will be contacted by the author (via e-mail).

2.2.2 Project Scope

The EUnetHTA Guidelines, available at https://www.eunethta.eu/methodology-guidelines/ **need to be consulted** throughout the assessment process.

Table 2-5: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	**Project Scope**
Population	**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** • 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) inability to use CPAP (greater than 5 nights per week of usage, usage defined as greater than 4 hours of use per night), or 2) unwilling to use CPAP (for example, a patient returns the CPAP system after attempting to use it or has claustrophia on 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 some long-term complications. Only patients who present inadequate adherence or failure to positive pressure systems are the target group of the intervention. [3, 4]. 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 [5]. 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 some 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 upper airway musculature, its acceptance rate among patients is low and the available evidence is not based on RCTs [6, 7].
Outcomes	<u>Effectiveness</u> • Apnoea-Hypopnoea 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) • Technical and Procedural Success • Rate of cardiovascular events • Rate of cerebrovascular events • Overall mortality • Adherence to treatment * Apnoea–Hypopnoea 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. It has been proposed a reduction of at least 50% from baseline in the AHI score and an AHI score of less than 20 events per hour to indicate 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 usual chances 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'. <u>Safety</u> 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 Instructions for Use, STAR trial and ADHERE registry [8, 9]
Study design	<u>Effectiveness:</u> Randomized clinical trials (RCTs), prospective non-randomized controlled studies, other observational comparative studies.

	Safety: Randomized clinical trials, prospective non-randomized controlled studies, other observational comparative and non- comparative studies, single arm studies with >10 patients.

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	*Internal Scoping Meeting: To internally discuss and reach consensus on the preliminary PICO*	January 2020	*e-meeting*	*Author(s), co-author(s), project manager, dedicated reviewer(s)*
		[DD/MM/YYYY]	*Additional e-meetings may be planned whenever needed*	*Author(s), Co-author(s), dedicated reviewer(s), project manager*
Feedback on draft submission file (optional)	*To point out the requirements for the final submission file by manufacturers*	*[DD/MM/YYYY]*	*E-mail*	*Author(s), project manager, manufacturers*
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*
Second draft of the rapid assessment	*To discuss comments from ≥ 2 external clinical experts and manufacturers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers; external experts, manufacturers*

3.3 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://eunethta.eu/rapid-reas/ .

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.

3.4 Collaboration with stakeholders

Collaboration with manufacturer(s)

There will be a review of the PICO and a fact check of the draft project plan and the draft assessment by the manufacturer(s).

Collaboration with other stakeholders

Patient involvement is intended. Several contacts with individual and organizations of patients have been made There is confirmation of participation from some patients. The process to obtain patient input will be “One-on-one conversation” through a semi structured interview [10].

Collaboration with EUnetHTA Work Packages (WP)

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the

involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.5 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised "Declaration of Interest and Confidentiality Agreement statements.

Author, co-author(s) and dedicated reviewers who declare a specific conflict of interest will be excluded from the whole work under this specific topic. However, they still may be included in other assessments.

For external experts, patients or other stakeholders involved, conflict of interest declarations are collected. External experts or patients who declare a specific conflict of interest will be excluded from parts of or the whole work under this specific topic. However, they still may be included in other assessments.

Manufacturer(s) will sign a Confidentiality Agreement form regarding the specific project.

4 References

1. Higgins JPT, Sterne JAC, Savovic J, Page MJ, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials. Cochrane Database of Systematic Reviews. 2016;10.

2. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

3. Chai-Coetzer CL, Luo YM, Antic NA, Zhang XL, Chen BY, He QY, et al. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. Sleep. 2013;36(12):1929-37.

4. Sarrell EM, Chomsky O, Shechter D. [Treatment compliance with continuous positive airway pressure device among adults with obstructive sleep apnea (OSA): how many adhere to treatment?]. Harefuah. 2013;152(3):140-4, 84, 83.

5. Calik MW. Treatments for Obstructive Sleep Apnea. J Clin Outcomes Manag. 2016;23(4):181-92.

6. Caples SM, Rowley JA, Prinsell JR, Pallanch JF, Elamin MB, Katz SG, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. Sleep. 2010;33(10):1396-407.

7. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Surgical treatment of snoring and obstructive sleep apnea. TEC Assessment 2019; 2019.

8. Heiser C, Steffen A, Boon M, Hofauer B, Doghramji K, Maurer JT, et al. Post-approval upper airway stimulation predictors of treatment effectiveness in the ADHERE registry. Eur Respir J. 2019;53(1).

9. Woodson BT, Strohl KP, Soose RJ, Gillespie MB, Maurer JT, de Vries N, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. Otolaryngol Head Neck Surg. 2018:1-9.

10. EUnetHTA. Patient Input in Relative Effectiveness Assessments Diemen (The Netherlands): EUnetHTA; 2018 [Available from: https://companionguide.eunethta.be/lib/exe/fetch.php?media=pharma:final_290519_patient-input-in-reas.pdf].

Appendix A

4.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 4-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What are the technology and the comparator(s)?	**Yes – critical**	M	What is Hypoglossal Nerve Stimulation (HGNS) in patients with moderate to severe obstructive sleep apnoea (OSA)? What are positive airway pressure (PAP) systems? What are other non-invasive procedures used in patients with moderate to severe obstructive sleep apnoea (OSA)?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking? [This assessment element can be placed either in the TEC OR in the CUR domain]	**Yes – critical**	M	For which indications has the HGNS received marketing authorisation or CE marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	**Yes**	M	What is the claimed benefit of HGNS in relation to the comparator(s)?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	**Yes**	NM	What is the phase of development and implementation of HGNS and comparators?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	**Yes**	M	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?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	**No**	NM	
B0009	Investments and tools required to	What equipment and supplies are needed to use the	**Yes**	NM	What equipment and supplies are needed to use HGNS and the comparators?

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
	use the technology	technology and the comparator(s)?			
A0021	Regulatory Status	What is the reimbursement status of the technology? [This assessment element can be placed either in the TEC OR in the CUR domain]	**Yes**	NM	What is the reimbursement status of HGNS?
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	**Yes – critical**	M	What is moderate to severe obstructive sleep apnoea (OSA) in the scope of this assessment?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	**Yes**	NM	What are the known risk factors for OSA?
A0004	Target Condition	What is the natural course of the disease or health condition?	**Yes**	M	What is the natural course of OSA?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	**Yes**	M	What are the symptoms and the burden of OSA?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	**No**	NM	
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	**Yes – critical**	M	How OSA is currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	**Yes – critical**	M	How OSA is currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	**Yes – critical**	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	**Yes**	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	**Yes**	M	How much is HGNS utilised?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	**Yes**	M	What is the expected beneficial effect of HGNS on mortality?
D0005	Morbidity	How does the technology affect symptoms and	**Yes – critical**	M	How does HGNS affect symptoms and findings (severity, frequency) of OSA?

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		findings (severity, frequency) of the disease or health condition?			
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	**Yes**	M	How does HGNS affect progression (or recurrence) of OSA?
D0011	Function	What is the effect of the technology on patients' body functions?	**Yes**	M	What is the effect of HGNS on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	**Yes**	NM	How does the use of HGNS affect activities of daily living
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	**Yes**	M	What is the effect of HGNS on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	**Yes**	M	What is the effect of HGNS on disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	**Yes**	NM	Were patients satisfied with HGNS?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	**Yes – critical**	M	How safe is HNSS in relation to comparators?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	**No**	NM	
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	**Yes**	M	How does the frequency or severity of harms change over time or in different settings?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	**Yes**	M	What are the susceptible patient groups that are more likely to be harmed through the use of HGNS?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	**Yes**	NM	Are HGNS and comparators associated with user-dependent harms?
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	**Yes**	M for medical devices	What kind of data/records and/or registry is needed to monitor the use of HGNS and comparators?

4.2 Checklist for potential ethical, organisational, patient and social and legal aspects

1. Ethical	
1.1. 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?	Yes
The use of HGNS would give rise to ethical issues related to equal access to the treatment. This intervention could not be available for every patient in need for it.	
1.2. Does comparing HGNS to the defined, existing comparators point to any differences that may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of HGNS and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	No
2.2. Does comparing HGNS to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
The use of HGNS could need training processes, or a learning curve	
3. Social	
3.1. Does the introduction of HGNS 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 HGNS to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4. Legal	
4.1. Does the introduction of HGNS and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing HGNS to the defined, existing comparator(s) point to any differences that may be legally relevant?	No