



Australian Government

Department of Health

Application Form

Hypoglossal nerve stimulation using the Genio System for the treatment of moderate to severe obstructive sleep apnoea in patients who have failed or are intolerant to continuous positive airways pressure

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: Nyxoah S.A.

ABN: REDACTED

Business trading name: REDACTED

Primary contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

Alternative contact name: REDACTED

Primary contact numbers

Business: REDACTED

Mobile: REDACTED

Email: REDACTED

2. (a) Are you a lobbyist acting on behalf of an Applicant?

Yes

No

(b) If yes, are you listed on the Register of Lobbyists?

Yes

No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Hypoglossal nerve stimulation using the Genio® System for the treatment of moderate to severe obstructive sleep apnoea (OSA) in patients who have failed or are intolerant to continuous positive airways pressure (CPAP).

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

OSA is a sleep condition where the muscles and soft tissues in the throat and tongue relax too much and collapse. This leads to repeated episodes of obstruction of the airway and cessation of breathing during sleep, in turn resulting in a reduction in blood oxygen saturation. Common symptoms of OSA are daytime sleepiness, restless sleep and loud snoring. Patients with OSA also have an increased risk of insulin resistance (Type 2 diabetes), dyslipidaemia, vascular disease and death.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The Genio® System is a medical device for the treatment of OSA. It has two key components:

- The Genio® Implantable Stimulator (IS). This device is implanted on the hypoglossal nerve during a surgical procedure of approximately 90 minutes (Lewis et al. 2019).
- The Activation Chip & Disposable Patch. The Activation Chip contains a rechargeable battery and activates the Genio® IS by wireless energy transmission while the patient is asleep

The Genio® System is designed to treat moderate to severe OSA patients via hypoglossal nerve stimulation (HNS). The hypoglossal nerve is the main nerve controlling tongue movement. Direct stimulation of this nerve via HNS moves the tongue forward and increases pharyngeal muscles tone. In turn, this prevents the collapse of the airway and maintains breathing space for the patient.

The Genio® System uses the same mechanism of action as another device currently being considered by MSAC, the Inspire® System (MSAC Application 1595).

6. (a) Is this a request for MBS funding?

Yes

No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

Amendment to existing MBS item(s)

New MBS item(s)

Given that the Genio® System and Inspire® System have the same mechanism of action, Nyxoah believe that simple amendments to the proposed MBS items for the Inspire® System outlined in MSAC Application 1595 would accommodate the medical services associated with the implantation and removal (if required) of the Genio® System and other HNS technologies that may seek funding in the future. This approach is also supported by two Australian experts (**REDACTED**), who have first-hand experience in the use of HNS systems. Separate letters from these experts are provided with this application.

If MSAC does not recommend listing medical services associated with the implantation and removal (if required) of the Inspire® System on the MBS after its consideration of Application 1595, then new MBS items for the Genio® System are requested.

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

MSAC assessment of the Inspire® System through Application 1595 is ongoing. The application was reviewed at the 5-6 December PASC meeting. As such, there are currently no existing MBS item numbers to be amended.

Amendments to the MBS item descriptors proposed for the Inspire® System in their MSAC Application 1595 that would accommodate the medical services associated with the implantation and removal (if required) of the Genio® System are outlined in Part 8 of this MSAC Application Form.

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Minor amendments to the item descriptor that does not affect how the service is delivered.

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)

As outlined above, if MSAC does not recommend listing medical services associated with the implantation and removal (if required) of the Inspire® System on the MBS after its consideration of Application 1595, then new MBS items for the Genio® System are requested.

(f) Is the proposed service seeking public funding other than the MBS?

Yes

No

(g) If yes, please advise:

The Genio® System requires the implantation of the IS component on the hypoglossal nerve during a surgical procedure. This application relates to the medical services provided by a surgeon associated with the implantation, programming, and removal (if required) of the IS device.

Private health insurance funding for the Genio® System will be sought separately via a submission to the Prostheses List Advisory Committee (PLAC).

7. What is the type of service:

- Therapeutic medical service
- Investigative medical service
- Single consultation medical service
- Global consultation medical service
- Allied health service
- Co-dependent technology
- Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service (*which could be one or more of the following*):

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

- Pharmaceutical / Biological
- Prosthesis or device
- No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

N/A

(b) if yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

N/A

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

- Yes
- No

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prosthesis List Advisory Committee (PLAC)?

Yes

No

Please be advised that if an expedited PASC pathway is deemed appropriate for this application, then Nyxoah intend to lodge a submission to have the Genio® System added to the Prosthesis List at the May 2020 deadline for PLAC listing date of November 2020.

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

Yes

No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

The Inspire® System is a similar medical device for the treatment of OSA using the same mechanism of action of HNS as the Genio® System. The Inspire® System is manufactured by Inspire Medical Systems Inc. and is the basis of an MSAC assessment through Application 1595 reviewed at the 5-6 December PASC meeting.

An additional HNS technology, LivaNova THN Sleep Therapy system, manufactured by LivaNova PLC is currently under development.

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables:

- Disposable patches. The Disposable Patch is a single-use medical grade adhesive patch placed on the skin under the chin. The Activation Chip is attached to the Disposable Patch at night, and together, they transmit energy to the Implantable Stimulator. After use, the Activation Chip can be detached from the Disposable Patch and the patch can be disposed of.
- External Stimulator: The External Stimulator is a disposable single-use device that is used during the surgical implantation procedure to test activation of the Implantable Stimulator and confirm its proper placement

Multi-use consumables:

- The Activation Chip constitutes the detachable power source of the IS and is composed of the user's personalised therapy program and a battery. The Activation Chip is used by the patient in order to achieve stimulation of the hypoglossal nerve during sleep. The same Activation Chip is used each night with patients charging the battery in the Activation Chip during the day with a proprietary charging unit.
- The Charging Unit. A proprietary charging unit and its power adapter are used to charge the Activation Chip's battery.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Active implantable medical device (AIMD)

Manufacturer's name: Nyxoah

Sponsor's name: REDACTED

- (b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

- Class III
 AIMD
 N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

- Yes
 No

- (b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

- Yes (if yes, please provide details below)
 No

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

- Yes (please provide details below)
 No

Date of submission to TGA: REDACTED

Estimated date by which TGA approval can be expected: REDACTED

TGA Application ID: REDACTED

TGA approved indication(s), if applicable: not applicable

TGA approved purpose(s), if applicable: not applicable

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Not applicable

PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). Please do not attach full text articles, this is just intended to be a summary.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication* **
1	Non-randomised trial	Bilateral hypoglossal nerve stimulation for treatment of adult obstructive sleep apnea (Eastwood et al. 2020)	This study reports the efficacy and safety of the Genio® System for the treatment of OSA. 27 patients were implanted with 6-month follow-up data available from 22 patients. At 6 months following implantation/activation the mean AHI was reduced by 10.8% (95% CI 14.6-7.0), p<0.0001. Improvements in other OSA-related endpoints were also reported.	https://erj.ersjournals.com/content/55/1/1901320.abstract	January 2020
2	Meta-analysis	The outcomes of hypoglossal nerve stimulation in the management of OSA: A systematic review and meta-analysis (Kompelli et al. 2019)	Meta-analysis of efficacy and safety outcomes for patients with OSA treated with HNS. Outcomes for 381 patients and 16 studies were included. At 6 months following implantation/activation the mean apnoea-hypopnea index (AHI) difference from baseline was -23.5% (95% CI -19.4 to -27.6), p<0.00001. Improvements in other OSA-related endpoints were also reported.	https://www.sciencedirect.com/science/article/pii/S2095881118300283	March 2019

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication* **
3	Meta-analysis	Hypoglossal nerve stimulation long-term clinical outcomes: a systematic review and meta-analysis (Costantino et al. 2019)	Meta-analysis of studies evaluating HNS clinical outcomes for the treatment of moderate-severe OSA. At 12 months, the AHI mean change was -17.50 and this was maintained at 5 years (-18.00). Only 6% of patients reported serious device-related adverse events after 1- and 5-year follow-up.	https://link.springer.com/article/10.1007%2Fs11325-019-01923-2	August 2019

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

*** If the publication is a follow-up to an initial publication, please advise.

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1	Non-randomised trial	Bilateral Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnoea With and Without Complete Concentric Collapse (BETTER SLEEP) ClinicalTrials.gov identifier: NCT03763682	This study will recruit approximately 40 patients with OSA from 4 Australian centres. Patients will have baseline AHI of 15-50 and have either not tolerated, have failed or refuse positive airways pressure treatments. The primary outcome measures are the incidence of serious device related adverse events recorded during the study (safety) and change in AHI from baseline to 6 months following implantation (efficacy).	https://clinicaltrials.gov/ct2/show/NCT03763682	Estimated study completion date January 2020

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

***Date of when results will be made available (to the best of your knowledge).

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

Australasian Sleep Association.

No change from Application 1595 (Inspire® System), which is currently under MSAC assessment, thus a further statement of clinical relevance is not applicable.

20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

Australasian Society of Otolaryngology, Head and Neck Surgery

Royal Australian College of Physicians (Respiratory Medicine and Sleep Medicine) as specified in Application 1595 (Inspire® System) which is currently under MSAC assessment.

21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

Sleep Disorders Australia.

Sleep Health Foundation as specified in Application 1595 (Inspire® System) which is currently under MSAC assessment.

22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

The Inspire® System and LivaNova THN Sleep Therapy are similar medical devices for the treatment of OSA using the same mechanism of action of HNS as the Genio® System.

The Inspire® System is manufactured by Inspire Medical Systems Inc and is the basis of an MSAC assessment through Application 1595 and currently going through the TGA regulatory process.

LivaNova THN Sleep Therapy system is manufactured by LivaNova PLC and is currently still in trial development and not yet available in Australia.

23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1: **REDACTED**

Name of expert 2: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED**

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

The Genio® System is intended for use in patients with moderate to severe OSA who have failed or are intolerant to continuous positive airways pressure (CPAP). This patient population is consistent with the patient population in which the Inspire® System is proposed to be used in Application 1595.

The classification of moderate to severe OSA applicable to this application is having an assessment of AHI ≥ 15 events/hour. A systematic review of the prevalence of OSA reported in 24 studies reports prevalence rates in adults with OSA and an AHI ≥ 15 of between 6%-17% (Senaratna et al. 2017). In 2010 it was estimated that there were 775,000 Australians with OSA based on AHI ≥ 15 (Deloitte Access Economics report for Sleep Health Foundation 2010). Moderate to severe OSA is reported at higher rates in patients with increased body mass index, older patients and males.

Patients with OSA suffer chronic fatigue and daytime sleepiness with significant impact on mood. Daytime concentration can be affected severely and there is evidence that people with OSA have a 2.5 fold increase in motor vehicle accidents (Sleep Health Foundation website). Untreated OSA is strongly associated with hypertension, insulin resistance (Type 2 diabetes) and dyslipidaemia with increased risks of myocardial infarction, stroke, depression and death. The impacts of OSA extend beyond the patient concerned through keeping sleeping partners awake which can also causes low mood and irritability.

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

There are no differences in the patient characteristics, approach to management or referral pathways associated with the Genio® System compared with the Inspire® System.

Prior to being considered for HNS therapy using either the Genio® System or Inspire® System a patient must:

- Be assessed as having high probability of moderate to severe OSA and referred to a sleep study based on questionnaire scores
 - STOP-Bang score of ≥ 4 or OSA50 score of ≥ 5 or positive Berlin Questionnaire, and
 - Epworth Sleepiness Scale ≥ 8
- Be diagnosed with OSA with AHI ≥ 15 as per the results of a sleep study
- Have failed or be intolerant to CPAP

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

A summary of the current clinical management pathway for patients before being eligible for HNS therapy using either the Genio® System or Inspire® System is provided in the table below.

Activity	Setting	Clinician(s) involved
Diagnostic work-up		
Presentation of patient with symptoms of OSA	Outpatient	General practitioner
Perform OSA screening questionnaires	Outpatient	General practitioner (if experienced) OR sleep specialist
Sleep study to confirm diagnosis of moderate to severe OSA (AHI ≥15)	Overnight stay in sleep clinic	Sleep specialist
Continuous positive airway pressure therapy		
Initiate CPAP	Patient home	General practitioner (if experienced) OR sleep specialist
Monitor symptoms and treatment adherence	Outpatient	General practitioner (if experienced) OR sleep specialist
Sleep study to assess treatment response (if lack of response indicated)	Overnight stay in sleep clinic	Sleep specialist
Referral for hypoglossal nerve stimulation therapy		
Presentation of patient with moderate to severe OSA refractory to CPAP	Outpatient	Surgeon with experience in implantation and use of HNS systems

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

The Genio® System is comprised of two key components:

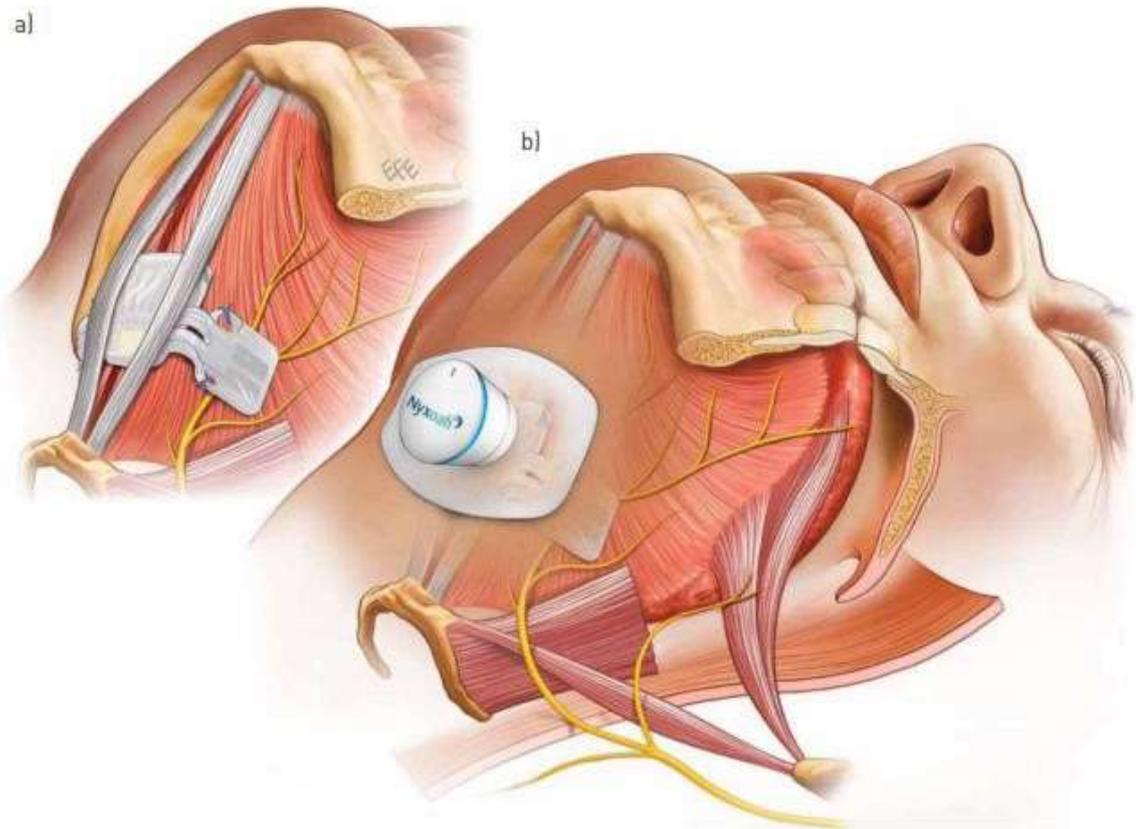
- The Genio® Implantable Stimulator (IS), and
- The Activation Chip & Disposable Patch. The Activation Chip contains a rechargeable battery and activates the Genio® IS by wireless energy transmission while the patient is asleep

In order to exert its therapeutic effect, the Genio® IS must be implanted in a patient such that it straddles the genioglossus muscles and hypoglossal nerve branches bilaterally. The key medical service relating to this MSAC Application is to have this implantation procedure listed on the MBS.

The key steps involved in the implantation of the Genio® IS are:

- Under general anaesthesia with nasotracheal intubation, the patient is placed in a supine position with the neck extended
- Electrodes connected to a nerve integrity monitoring system are inserted into the tongue. These assist in the location of the medial branches of the hypoglossal nerve and to verify proper muscle contraction
- A transverse incision (approximately 6 cm) is made midway between the mentum and the hyoid bone
- The vertical fibres of the geniohyoid (GH) muscles are identified and then separated
- After separation of the GH muscles, the genioglossus (GG) muscles are identified and the fat lateral to it is explored to find the hypoglossal nerve
- The hypoglossal nerve is dissected cleanly on its superior aspect, and a deep pocket made superior to the nerve to fit the legs of the Genio® IS
- The Genio® IS is placed into position, ensuring that the hypoglossal nerve passes across both electrodes
- Upon satisfactory positioning intraoperative testing of the stimulation effect is performed using an external stimulator
- Upon confirmation of stimulation effect the Genio® IS is fixed in place by suturing to the GG muscles (both sides)
- Skin edges are then temporarily closed and covered with a sterile plastic sheet. Confirmation of the correct positioning of the Genio® IS takes place using the Activation Chip. Responses on the nerve monitoring system and visualisation of movement of the tongue, epiglottis and palate observed through an endoscope is confirmatory of successful implantation of the Genio® IS
- Upon successful implantation of the Genio® IS the muscles are reapproximated and closed with sutures and the skin is closed and a waterproof dressing is applied.

Visual representation of the placement of the Genio® IS on the hypoglossal nerve (panel A), as well as the Activation Chip used to stimulate the nerve during sleep (panel B) is provided in the figure below.



28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

REDACTED

A high level comparison of the Genio® System and Inspire® System is presented below.

	Genio® System	Inspire® System
Implantable parts	1 implantable part	3 implantable parts Pulse generator Cuff electrode Respiratory sensor
Number of incisions required for implantation	One	Three
Lead tunnelling required	None	Two: from submandibular area of chest to connection with pulse generator and from the intercostal space to the chest
Stimulation targets	Hypoglossal nerve	Hypoglossal nerve
Type of stimulation	Bilateral: left and right	Unilateral

While there are differences in Genio® System and Inspire® System, these are considered to be relatively minor and the MBS items and descriptors for implantation should be the same for both products. This is because both systems are intended for the treatment of OSA in essentially the same patient population and use the same mechanism of action of HNS. Both systems require the implantation of components in order to exert their clinical effect, with the nerve stimulator/pulse generator the key component responsible for stimulating the hypoglossal nerve.

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Yes. The Genio® System is designed to treat patients with moderate to severe OSA who have failed or who are intolerant of CPAP. Patients indicated for the therapy are those with an AHI ≥ 15 and ≤ 65 . Patients who have a complete concentric collapse at the soft palate level are not considered suitable.

The subgroup as described here for the Genio® System is the same patient population as for the Inspire® System.

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Yes. Patients would be required to have a confirmed diagnosis of moderate to severe OSA (AHI ≥ 15) as determined by a sleep study, have failed or be intolerant to CPAP and to be suitable surgical candidate for the procedure (patients with complete concentric collapse at the soft palate level are not considered suitable) prior to be eligible to access treatment using the Genio® System.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Medical services relating to general anaesthesia would need to be delivered at the same time as the implantation of the Genio® IS.

32. If applicable, advise which health professionals will primarily deliver the proposed service:

Ear, nose and throat or head and neck surgeon with suitable training in the implantation of the Genio® device.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

The implantation of the Genio® IS should not be delegated or referred to another professional for delivery.

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

It is proposed that funding for the implantation of the Genio® IS through the MBS would be limited to clinicians with sufficient expertise in surgical procedures in the head and neck areas.

No limitations are proposed on who might provide a referral for implantation of the Genio® IS and use of the Genio® System. It is anticipated that the general practitioner or sleep specialist which has been monitoring a patient with moderate to severe OSA receiving treatment with CPAP would refer the patient to the relevant specialist upon CPAP failure or intolerance.

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Registered ear, nose and throat or head and neck surgeons will have met the formal training and qualifications required to undertake surgical procedures associated with the implantation of the Genio® IS.

User training plans for the Genio® System have been developed by Nyxoah and all healthcare professionals and patients will undergo relevant training prior to the use of the Genio® System.

The minimal training requirements and competencies required of healthcare professionals involved in implanting or handling the Genio® System are outlined below. Nyxoah will be the party responsible for the delivery of these training activities.

	Sleep Physician	Surgeon	Sleep Lab technician
Genio® System concept and technology	X	X	X
Patient Instructions (Genio® System - Patient IFU)	X		X
Genio system Programming (Genio® System - Technical Sleep Lab IFU)	X		X
Implant Procedure (Genio® System - Surgeon IFU)	X (Optional)	X	
Surgeon Practical Training course including Cadaver Lab		X	

Abbreviation: IFU=Instructions For Use

All healthcare professionals interacting with patients will receive instructions on how to train a patient to use the Genio® System at home following the activation of their unit. Patients will also be supplied with the 'Genio® System – Patient Instructions For Use' document which contains detailed instructions of use and placement of the Disposable Patch, Activation Chip and use of the Charging Unit. During each patient follow up visit at the clinic, daily use will be checked and patient re-trained if deemed necessary.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms – GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)

- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Pre-implantation medical history and suitability assessment for the Genio® System would take place in the consulting rooms of an ear, nose and throat or head and neck surgeon with expertise in treating patients with OSA with HNS therapy.

Implantation of the Genio® IS would take place as part of an inpatient episode at a private or public hospital.

Post-implantation follow-up and activation/programming of the Genio® System would take place in the consulting rooms of a specialist clinician with expertise in treating patients with OSA with HNS therapy.

Application of the Activation Chip would take place in the patients home each night prior to the patient going to sleep.

37. Is the proposed medical service intended to be entirely rendered in Australia?

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

Given that the Inspire® System is already being considered as part of the MSAC process under application item 1595, it is proposed that the Inspire® System is the appropriate comparator for the Genio® System. The patient population and mechanism of action are the same for both systems and patient relevant patient outcomes are similar based on the clinical evidence base.

Note the Inspire® application nominated conservative management and to a lesser extent surgical intervention as the comparators in this MSAC Application.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

- Yes (please list all relevant MBS item numbers below)
- No

The Inspire® System is currently under assessment by MSAC through Application 1595. Simple amendments to MBS items for the Inspire® System outlined in MSAC Application 1595 would accommodate the medical services associated with the implantation and removal (if required) of the Genio® System and any future HNS technologies that apply for funding.

40. Define and summarise the current clinical management pathway/s that patients may follow after they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

The post-implantation clinical management pathway for patients treated with the Genio® System is consistent with the clinical management pathway for patients treated with the Inspire® System (comparator). A summary of the management of patients after the implantation of the components of both HNS systems is provided in the table below.

Activity	Genio® System		Inspire® System	
	Setting	Clinician(s) involved	Setting	Clinician(s) involved
Post-implantation follow-up and device activation/programming	Outpatient	Implanting surgeon	Outpatient	Implanting surgeon
Ongoing patient monitoring/re-programming	Outpatient	Implanting surgeon OR sleep specialist	Outpatient	Implanting surgeon OR sleep specialist
Removal or repositioning of nerve stimulator/pulse generator (if required)	Inpatient	Implanting surgeon	Inpatient	Implanting surgeon
Removal or repositioning of lead (if required)	Not required (component not used)		Inpatient	Implanting surgeon
Removal or repositioning of respiratory sensing lead	Not required (component not used)		Inpatient	Implanting surgeon
Replacement of nerve stimulator/pulse generator battery	Not required (uses external battery)		Inpatient	Implanting surgeon

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

- In addition to (i.e. it is an add-on service)
 Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

The decision to use any given HNS system for the treatment of patients with moderate to severe OSA is likely to be driven by individual surgeon experience or preference. Patients will also have a view on what type of HNS system might be more preferable. As such, it is not yet possible to reliably estimate the extent to which the Inspire® System will be substituted with the Genio® System in broader clinical practice.

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

Given that the Genio® and Inspire® Systems are similar there are expected to be no new changes in service delivery with the introduction of the Genio® System. For more detail please refer to information provided in response to question 40.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

A clinical claim that HNS therapy using the Genio® System results in a similar change from baseline in Apnea Hypopnea Index (AHI) and other important clinical endpoints at 6-months following implantation compared with the Inspire® System is foreshadowed.

It is further foreshadowed that the rate of device related and other adverse events reported for the Genio® System will be consistent with the rates reported for the Inspire® System.

44. Please advise if the overall clinical claim is for:

- Superiority
- Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Device related adverse events

Other adverse events

Clinical Effectiveness Outcomes:

Apnoea Hypopnoea Index (AHI): change from baseline

Oxygen Desaturation Index (ODI): change from baseline

Epworth Sleepiness Scale (ESS): change from baseline

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

There is no recent epidemiological study in Australia that can provide accurate estimates of the number of patients that would be eligible for implantation of HNS technology under the proposed use of the product. In 2010 it was estimated that there were 775,000 Australians with OSA based on $AHI \geq 15$ (Deloitte Access Economics report for Sleep Health Foundation 2010).

To determine the number of patients eligible for HNS technologies (and thus Genio® or Inspire® systems) there are a number of steps that need to be taken, including:

- Incidence/prevalence OSA (% of population)
- Proportion of above who seek testing for OSA
- Proportion of above with moderate-to-severe OSA
- Proportion of moderate to severe patients who have CPAP
- Proportion of patients with CPAP that either fail or intolerant of such therapy
- Patients suitable for HNS treatment

There are some data gaps in determining eligibility for treatment with HNS. For example, a data gap is identifying the number of patients in Australia who have CPAP, and the proportion of patients who have failed or are intolerant to CPAP. There are currently no Commonwealth programs which assist patients to purchase CPAP machines. Subject to availability, funding for CPAP machines and related equipment may be available through the state/territory programs. Eligibility criteria for funding varies between programs, but generally funding is restricted to patients with a long-term or permanent disability or who are frail and aged.

There are 2 MBS items 12203 and 12250 that are applicable for patients who require a diagnostic sleep study. They enable direct GP referral to testing without personal assessment by a sleep or respiratory physician, when validated screening questionnaires suggest a high pre-test probability for diagnosis of symptomatic, moderate to severe OSA.

The table below is taken from Application 1595 (Inspire® System) which is currently under MSAC assessment. The figure of 22,610 indicates the potential new eligible patients for HNS per year based on 2017/18 MBS sleep study data.

Overall, this table represents a reasonable methodological approach to the estimation of eligible patient population. However, as outlined above the estimated population could be made more certain with the availability of robust data pertaining to the number of patients receiving CPAP treatment each year. As stated earlier, this data is difficult to access in the public domain but will be available to private insurance and the sponsors of CPAP technology. The application of parameters relating to BMI in the estimated prevalent population in Application 1595 is a further source of uncertainty as this is not specified as being a clinical criteria for a patient being eligible to access HNS.

Note that the overall size of the prevalent population suitable for HNS would not be meaningfully different regardless of whether the Inspire® System and/or Genio® System are available. Whilst Nyxoah believe that the estimates outlined in Application 1595 may not be truly reflective of the actual prevalent patient pool, it is committed to presenting a robust assessment of the estimated use of HNS in Australian practice as part of its submission to MSAC.

Description	Source	Estimated Population
Annual Sleep Studies	MBS items 12203 and 12250	182,965
55.8% with diagnosis of moderate to severe OSA	Gray et al 2017	102,094
50% failure of CPAP	Australasian Sleep Association	51,047
98.5% > 22 years	Medicare Australia Statistics	49,542
45.1% BMI < 30	Gray et al 2017	22,343
10% adjustment for patients with BMI ≥ 30 < 32	Assumption	24,577
Exclude 8% of patients with complete concentric collapse	Strollo et al 2014	22,610

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

The implantation of the Genio® IS is only required once per patient per course of treatment
In a small number of circumstances (e.g. due to development of post-implantation infection), patients may also require the removal or repositioning of the Genio® IS. It is anticipated that this would only occur once per patient per course of treatment.

48. How many years would the proposed medical service(s) be required for the patient?

The use of HNS for the treatment of OSA is ongoing. No upper-limit to the number of years of use of the Genio® System is proposed.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Application 1595 (Inspire® System) projects that 45 patients will initiate HNS in the first full year (2021), rising to 153 patients in 2023. Nyxoah do not believe that these estimates are reasonable based on the substantial prevalent patient population (22,610 outlined in Application 1595) and that a higher number of patients is likely to utilise HNS if available through the MBS.

Nyxoah is committed to presenting a robust estimate of the uptake of HNS, as well as the split of use across the Genio® System and Inspire® System as part of its submission to MSAC. It is anticipated that this will be based on input from clinical centres with experience in the management of moderate to severe OSA refractory to CPAP.

Whilst Nyxoah believe that the uptake of HNS outlined in Application 1595 (Inspire® System) may be underestimated, it is not foreseen that there will be a meaningful incremental increase in the uptake of HNS with the availability of the Genio® System as an alternative option to the Inspire® System. This is because both systems are indicated in the same patient population and would be able to be implanted under the same MBS items (refer to question 52).

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

Refer to response to question 49.

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

An overview of the medical procedures associated with the use of the Genio® System and Inspire® Systems is provided below. Based on the MBS fee proposed in Application 1595, the leadless design of the Genio® System results in a reduction in the overall cost of MBS items using the Genio® System versus the Inspire® System.

Procedure	Genio® System	Inspire® System	MBS item/fee in MSAC Application 1595
Subcutaneous placement of electrical pulse generator	Required	Required	\$346.05
Surgical placement of lead	Not required	Required	\$684.95
Surgical placement of respiratory sensing lead	Not required	Required	\$684.95
Post-implantation programming	Required	Required	Not specified Programming of vagus nerve stimulation therapy via MBS item 40707: \$192.75
Removal/repositioning of electrical pulse generator	Required (if indicated)	Required (if indicated)	\$161.95
Removal/repositioning of lead	Not required	Required (if indicated)	Not specified Removal/repositioning of vagus nerve stimulation therapy lead via MBS item: \$615.05
Removal/repositioning of respiratory sensing lead	Not required	Required (if indicated)	Not specified Removal/repositioning of vagus nerve stimulation therapy lead via MBS item: \$615.05

52. Specify how long the proposed medical service typically takes to perform:

Advice from an Australian clinician experienced in the implantation of the Genio® IS is that the total operating time is approximately 90 minutes.

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Consultation with clinicians experienced in the management of patients with OSA using HNS therapy was undertaken during the preparation of this MSAC Application Form. Clinicians have advised that there is a preference for MBS items for HNS treatment not be specific to any given system and should be worded to accommodate the use of the Inspire® System, the Genio® System, or any other HNS systems that become available in the future.

Based on this clinician feedback, the following amendments (strikethrough text) to the MBS item descriptors outlined in Application 1595 are proposed.

Category 3 – Therapeutic Procedures

Proposed item descriptor: ~~Closed Loop hypoglossal nerve stimulation therapy with Inspire® Upper Airways Stimulation System~~ **Nerve stimulation therapy** through stimulation of the hypoglossal nerve, subcutaneous placement of electrical pulse generator for management of moderate to severe obstructive sleep apnoea in a patient who:

- a) has an Apnoea Hypopnoea Index of greater than 15 ~~and less than 65~~
- b) is aged 22 and over
- c) has failed or is intolerant to continuous positive airways pressure therapy.
- ~~d) does not have complete concentric collapse of the upper airway~~

Fee: \$346.05

The rationale for proposed amendments is that:

- Removal of reference to the Inspire® Upper Airways Stimulation System would allow the same MBS item to be used to implant the electrical pulse generator from any HNS system
- Removal of the restrictions based on having AHI <65 and not have complete concentric collapse of the upper airway are artefacts of the clinical criteria applied in clinical trials of the Inspire® Systems. Clinicians advised that there is no biological basis as to why OSA patient with an AHI >65 or complete concentric collapse of the upper airway would not obtain clinical benefit from HNS therapy

Category 3 – Therapeutic Procedures

Proposed item descriptor: ~~Closed loop hypoglossal nerve stimulation therapy with Inspire® Upper Airways Stimulation System~~ **Nerve stimulation therapy** through stimulation of the hypoglossal nerve, surgical repositioning or removal of electrical pulse generator inserted for management of moderate to severe obstructive sleep apnoea. ~~in a patient who:~~

- ~~a) has an Apnoea Hypopnoea Index of greater than 15 and less than 65~~
- ~~c) is aged 22 and over~~
- ~~d) has failed or is intolerant to continuous positive airways pressure therapy~~
- ~~e) does not have complete concentric collapse of the upper airway~~

Fee: \$161,95

The rationale for proposed amendments is that:

- Removal of reference to the Inspire® Upper Airways Stimulation System would allow the same MBS item to be used to reposition or remove the electrical pulse generator from any HNS system
- Clinical criteria are more appropriate to establish baseline patient eligibility at the implantation stage. Patients who are experiencing benefit from HNS with an AHI <15 may require repositioning or removal of the electrical pulse generator for reasons not related to OSA (e.g. infection). This service would not be eligible through the proposed MBS item descriptor in Application 1595.

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Attachment: Clinical management algorithms

Figure 1: Clinical management algorithm before moderate to severe OSA patients considered for HNS therapy

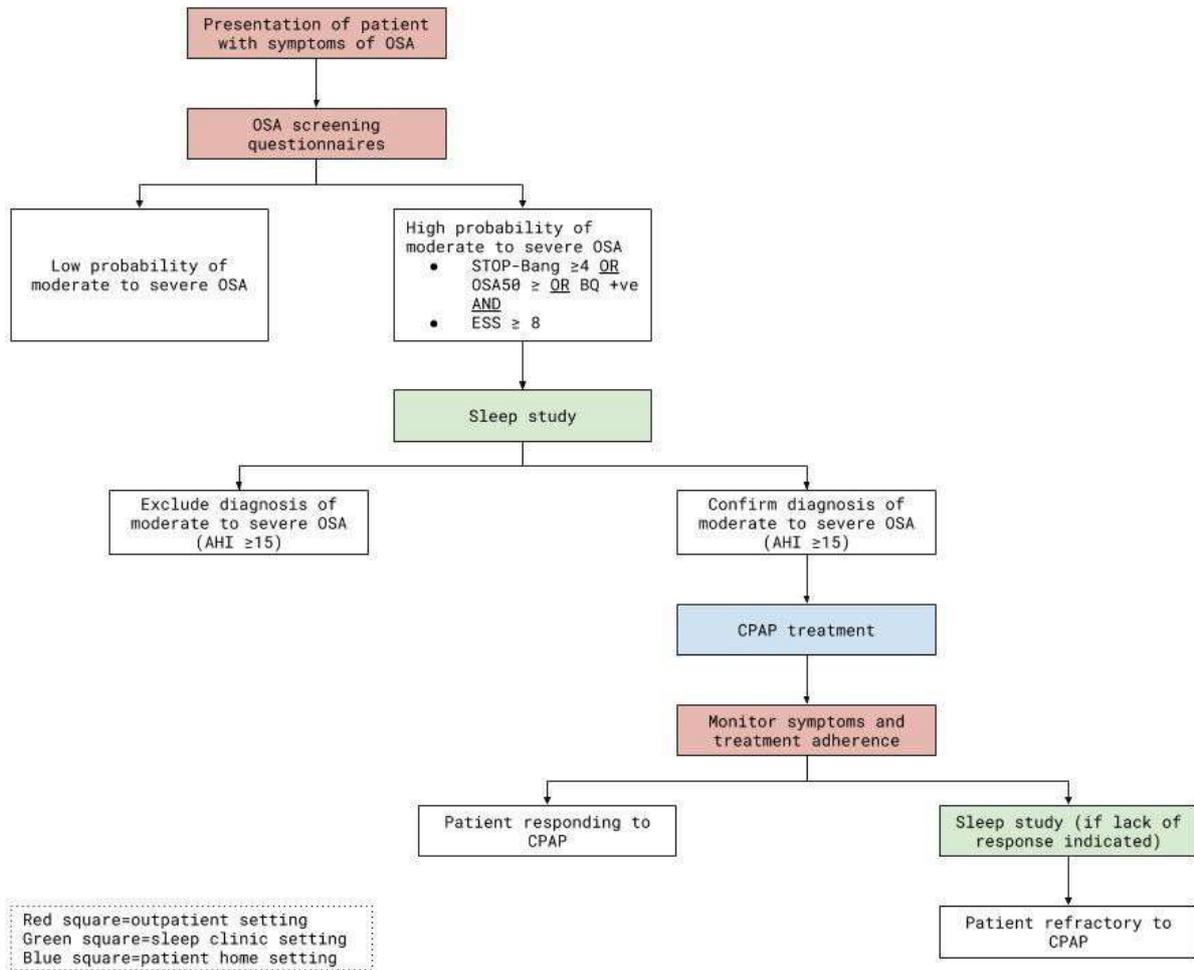


Figure 2: Clinical management algorithm for moderate to severe OSA patients receiving HNS therapy

