Australian Government

Department of Health

MSAC Application 1595.1

Closed-loop upper airway stimulation for moderate to severe obstructive sleep apnoea, for patients who have failed or are intolerant to continuous positive airway 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: Inspire® Medical Systems Inc
ABN: At present Inspire® Medical Systems does not have an entity in Australia **REDACTED**
Business trading name: Inspire® Medical Systems Inc

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative 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

Rationale for this Application

This application is being submitted following a post-MSAC meeting with the MSAC secretariat. The meeting was held to discuss the possibility of a resubmission of application 1595. MSAC did not recommend funding for the intervention described in application 1595 but described issues to address in any subsequent submission. The MSAC Secretariat informed us that the best approach would be to submit a new application form to determine the most appropriate pathway for any resubmission.

The applicant is seeking a fit-for-purpose pathway so that the applicant can proceed directly to ESC consideration without any additional consideration by PASC.

3. Application title

Closed Loop Upper Airways Stimulation (UAS) for Moderate to Severe Obstructive Sleep Apnoea (OSA) for 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)

Obstructive Sleep Apnoea (OSA) with Apnoea Hypopnoea Index (AHI) of greater than or equal to 15 in patients who have failed or are intolerant to CPAP therapy.

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)

Implantation of an Upper Airways Stimulator System. The system includes a respiratory sensing lead that senses breathing patterns. The respiratory sensing lead is linked to an implantable pulse generator that delivers mild stimulation to the hypoglossal nerve via a stimulation lead.

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)

(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:

Not applicable

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

N/A

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

N/A

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

☐ Yes
☒ No

(g) If yes, please advise:

N/A

7. What is the type of service:

Therapeutic medical service

8. **For investigative services, advise the specific purpose of performing the service**

N/A

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 Prostheses List Advisory Committee (PLAC)?

☐ Yes
☒ No

(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):

There have been devices manufactured that stimulate the hypoglossal nerve, however none have included a respiratory sensing lead. To our knowledge, these devices are not available for sale in Australia at present.

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

Single use consumables: A tunnelling tool is included in the Inspire® System.
Multi-use consumables: Not applicable

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: Implantable sleep apnoea treatment system
Manufacturer's name: Inspire® Medical Systems.
Sponsor's name: Plexus RA Pty Ltd

(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 (If yes, please provide supporting documentation as an attachment to this application form)
☒ 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

ARTG listing, registration or inclusion number: 340934, 340933, 340932, 340931, 340930. There are 5 registered components of the Inspire® System. These are:

Inspire Sleep Remote Model 2500
Inspire Physician Programmer Model 2740
Inspire Respiratory Sensing Lead Model 4340
Inspire Stimulation Lead Model 4063
Inspire IV Implantable Pulse Generator

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

1. 'The Inspire Sleep Remote Model 2500 is part of the Inspire Upper Airway Stimulation therapy system that is intended to treat moderate to severe obstructive sleep apnoea (15 AHI -65 AHI), in patients who are not effectively treated by, or able to tolerate, positive airway pressure (PAP) therapies, by improving airway patency through stimulation of the hypoglossal nerve, synchronous with respiration, to elicit a neuromuscular response at the base of the tongue.

2. The Inspire Physician Programmer Model 2740 is part of the Inspire Upper Airway Stimulation therapy system that is intended to treat moderate to severe obstructive sleep apnoea (15 AHI – 65 AHI), in patients who are not effectively treated by, or able to tolerate, positive airway pressure (PAP) therapies, by improving airway patency through stimulation of the hypoglossal nerve, synchronous with respiration, to elicit a neuromuscular response at the base of the tongue.

3. The Inspire Respiratory Sensing Lead Model 4340 is part of the Inspire Upper Airway Stimulation therapy system that is intended to treat moderate to severe obstructive sleep apnoea (15 AHI- 65 AHI), in patients who are not effectively treated by, or able to tolerate, positive airway pressure (PAP)

therapies, by improving airway patency through stimulation of the hypoglossal nerve, synchronous with respiration, to elicit a neuromuscular response at the base of the tongue.

4. The Inspire Stimulation Lead Model 4063 is part of the Inspire Upper Airway Stimulation therapy system that is intended to treat moderate to severe obstructive sleep apnoea (15 AHI – 65 AHI), in patients who are not effectively treated by, or able to tolerate, positive airway pressure (PAP) therapies, by improving airway patency through stimulation of the hypoglossal nerve, synchronous with respiration, to elicit a neuromuscular response at the base of the tongue.

5. The Inspire IV Implantable Pulse Generator Model 3028 is part of the Inspire Upper Airway Stimulation therapy system that is intended to treat moderate to severe obstructive sleep apnoea (15 AHI – 65 AHI), in patients who are not effectively treated by, or able to tolerate, positive airway pressure (PAP) therapies, by improving airway patency through stimulation of the hypoglossal nerve, synchronous with respiration, to elicit a neuromuscular response at the base of the tongue.

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?

N/A

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?

N/A

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**	**Short description of research**	**Website link to journal article or research**	**Date of publication**
1.	Multicentre prospective, single-group, cohort design. Consecutive responsive participants were included in a randomised controlled therapy-withdrawal trial	Strollo PK, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie B, Woodson T, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP 'Upper-Airway Stimulation for Obstructive Sleep Apnea' N Engl J Med 2014; 370:139-49	126 patients were surgically implanted with an upper airway stimulation device. There were significant improvements in primary outcome measures that included apnea-hypopnea index (AHI), oxygen desaturation index (ODI). Secondary outcome measures also improved including the Epworth Sleepiness Scale (ESS), and the Functional Outcomes of Sleep Questionnaire (FOSQ) and % of sleep time with O^2 saturation < 90%	NEJM	Multicentre prospective, single-group, cohort design. Consecutive responsive participants were included in a randomised controlled therapy-withdrawal trial

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
2.	Multicentre, prospective and retrospective observational registry	Heiser C, Steffen A, Boon M, Hofauer B, Dofhramji K, Maurer JT, Sommer JU, Soose R, Strollo PJ, Schwab R, Thaler, E Withrow K, Kominsky A, Larsen C, Kezirian EJ, Hsia J, Chia S, Hareick J, Strohl K, Mehra R 'Post-Approval Upper Airway Stimulation Predictors of Treatment Efficacy in the Adhere Registry' doi:10.1183/13993003.01405-2018	International multinational registry. 508 patients who had received upper airways stimulation were enrolled in 14 centres. Data collected included patient characteristics, AHI, ESS, objective adherence, adverse events and patient satisfaction measures	Euro Resp Journ	2018
	Multicentre prospective observational study	Thaler E, Schwab R, Maurer J, Soose R, Larsen C, Stevens S, Stevens D, Boon M, Huntley C, Doghramji K, et al *'Results of the ADHERE Upper Airway Stimulation Registry and Predictors of Therapy Efficacy.'* Laryngoscope 130:1333-1338, 2020	Multinational registry 1,017 patients who received upper airways stimulation were enrolled in 14 centres. 640 patients completed 6 months and 382 completed 12 months. Data collection includes AHI, ESS, adherence, adverse events and patient satisfaction.	https://onlinelibrary.wiley.com/doi/epdf/10.1002/lary.28286	May 2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	Cost-Effectiveness Analysis of the Upper Airway Stimulation for the treatment of OSA	Pietzsch JB, Lui S, Garner AM, Kezirian EJ, Strollo PJ 'Long-Term Cost-Effectiveness of Upper Airway Stimulation for the Treatment of Obstructive Sleep Apnea: A Model-Based Projection Based on the STAR Trial' SLEEP 2015:38(5): 735-744	5-State Markov model was used to predict cardiovascular endpoints (myocardial infarction, stroke, hypertension), motor vehicle collisions and QALYS and costs of UAS versus no treatment	SLEEP	Cost-Effectiveness Analysis of the Upper Airway Stimulation for the treatment of OSA
4.	Multicentre prospective single arm study of UAS for moderate to severe sleep apnoea	Steffen A, Sommer JU, Hofauer B, Maurer JT, Hasselbacher K, Heiser C, 'Outcomes After One Year of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Post-Market Study' Laryngoscope, 00:000-00, 2017	60 patients were followed for 12 months measuring home sleep test results and patient-reported outcome measures.	https://onlinelibrary.wiley.com/doi/abs/10.1002/lary.26688	May 31 2017
5.	Parallel arm experimental study prospective study	Mehra R, Steffen A, Heiser C, et al. *'Upper Airway Stimulation versus Untreated Comparators in Positive Airway Pressure Treatment Refractory Obstructive Sleep Apnea'* Am J Otolaryngol. 2020 Nov-Dec;41(6):102616. Doi: 10.1016/j.amjoto.2020.102616. Epub 2020 Jun 25. PMID:32645535	Consecutive participants with medical insurance with OSA and PAP intolerance were enrolled. If insurance was approved for UAS then patient was enrolled in therapy arm. If insurance was denied, patient was enrolled in control arm	https://pubmed.ncbi.nlm.nih.gov/32663043/	December 2020

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	Short description of research	Website link to research	Date
1.	Prospective, multi-centre randomised, crossover study including 100 participants.	Effect of Upper Airway Stimulation in Patients with Obstructive Sleep Apnea (EFFECT) ClincialTrials.gov Identifier: NCT03760328	Patients will be enrolled following 6 months of being implanted with the Inspire device. Patients will then be randomised to either therapeutic stimulation or sham stimulation. During the second phase the of the study the therapy settings will be crossed over	NCT03760328	Anticipated June or July 2021
2.	Double-blind sham-controlled randomised crossover trial of 10 weeks duration.	Cardiovascular endpoints for obstructive sleep apnea with 12th cranial nerve stimulation (CARDIOSA-12) ClincialTrials.gov Identifier: NCT03359096	Patients will be assigned to active or sham HGNS therapy. Primary outcome is 24 -hour ambulatory blood pressure. Secondary outcome is diastolic BP, nocturnal systolic and diastolic BP, sympathetic nerve activity, pre-ejection period, flow-mediated dilation and pulse wave velocity	NCT0335906	2021

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

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

    Royal Australian College of Physicians (Respiratory Medical and Sleep Medicine)

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

    Sleep Health Foundation was the only group that was identified. They are a charitable organisation and are not representative of consumers.

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

    Liva Nova, Apnex Medical supply hypoglossal nerve stimulators, however these are 'open loop' systems without a respiratory sensing lead. Nyxoah also supplies a hypoglossal nerve stimulator which is open loop and employs an external activation chip. To our knowledge none of these devices are currently available for sale 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**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

    Name of expert 2: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

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 Inspire® Upper Airways Stimulation (UAS) System is intended to be used in adult patients who have been confirmed to have moderate to severe obstructive sleep apnoea (OSA) and who have also been confirmed to have failed or cannot tolerate continuous positive airways pressure (CPAP) therapy or bi-level positive airway pressure (BIPAP) therapy and who do not have concentric collapse at the soft palate level and are currently untreated.

Most patients who would seek closed loop UAS are likely to remain untreated if closed loop UAS was not available. MSAC expressed concern that the potential population would be quite large. We have suggested the modification of 'currently remain untreated' to more accurately target the likely population for closed loop UAS in Australia.

Moderate to severe OSA is defined as having an Apnoea Hypopnea Index (AHI) of greater than or equal to 15 and less than or equal to 65. AHI measures the number of apnoea episodes per hour of sleep. Failure of continuous positive airway pressure (CPAP) therapies is defined as an inability to eliminate OSA (AHI of greater than 20 despite CPAP usage) and 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. Unwillingness to use CPAP (for example, a patient returns the CPAP system after attempting to use it).

OSA is a disorder of sleep which is characterised by repeated upper airway obstructions during the night, with resultant oxygen desaturations and arousals. OSA occurs when breathing is repetitively interrupted during sleep due to collapse of the upper airway. An apnoea is defined as a complete cessation of breathing lasting 10 seconds or greater. Approximately 10% of middle-aged men and 5% of middle-aged women in the general population are likely to have OSA (defined as > 10 obstructed breathing events/hour of sleep)[1]. Deloitte Access Economics[2] estimated in 2011 the Australian prevalence of OSA with ≥ 15 AHI to be 2.2% for women, 7.2% for men with an overall prevalence of 4.7%. The Sleep Health Survey of Australian Adults in 2016[3] estimates that doctor diagnosed sleep apnoea is 8.3% overall (men-12.9% and women 3.7%).

Cross sectional and longitudinal studies have suggested that moderate to severe OSA is independently associated with greater risk of all-cause mortality after adjustment for age, gender, mean arterial pressure, total cholesterol, high density lipo-protein cholesterol, body mass, diabetes, angina and smoking status[4] and a higher incidence of fatal and non-fatal cardiovascular events in patients with severe disease[5].

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[1] Young T et al *'Predictors of sleep-disordered breathing in community-dwelling adults: The Sleep Heart Health Study.'* Archives of internal medicine 2002; 162 (8): 893-900

[2] '*Re-awakening Australia. The economic cost of sleep disorders in Australia 2010*' for the Sleep Health Foundation October 2011. Deloitte Access Economics.

[3] Adams R et al *'Report to the Sleep Health Foundation 2016 Sleep Health Survey of Australian Adults'.*

[4] Mashall NS et al *'Sleep Apnea as an Independent Risk Factor for All-Cause Mortality: The Busselton Health Study'* Sleep 2008 Aug 1; 31(8): 1079-1085

[5] Marin JM *'Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study'* Lancet Vol 365, Iss 9464, P1046-1053, March 19, 2005

OSA is also associated with daytime sleepiness and an increased incidence of road accidents[6]. Overall OSA that is unable to be treated by CPAP represents a significant societal burden.

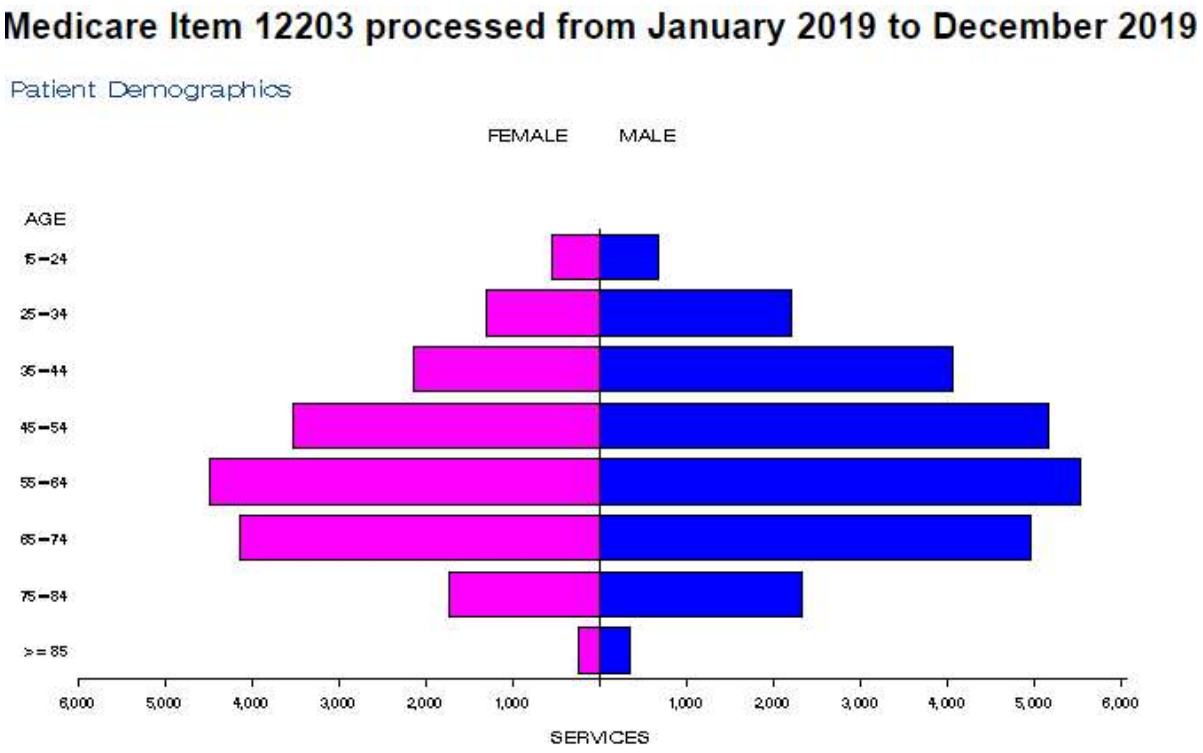
25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being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

OSA is more likely to occur in men than in women with a variety of prevalence studies consistently finding the disorder is more common in men. An Australian study, of men only, found that OSA was associated with older age, obesity, chronic obstructive airways disease, diabetes, asthma, hypercholesterolemia, and hypertension, and other lifestyle related disorders. There are no specific item numbers on the Medical Benefits Schedule for the treatment of OSA. Therefore, it is difficult to accurately assess the demographic profile of Australians being treated for OSA. it is also likely that hospital admissions are for sleep investigations rather than treatment of OSA. It is therefore more useful to look at the demographics of those Australians undergoing sleep investigation for demographic detail.

There are two item numbers that relate to adult sleep investigations. Although it cannot be at all certain whether these people will receive a diagnosis of OSA, it is nevertheless a snapshot of those seeking treatment for sleep disorders.

MBS Item 12203 is a Level 1 Sleep Investigation. This item number was claimed 43,385 times in the 2019. 2019 statistics have been used here as many sleep clinics were closed in 2020 due to the COVID-19 pandemic and are likely to be unrepresentative. Please see the demographic distribution below in Figure 1.

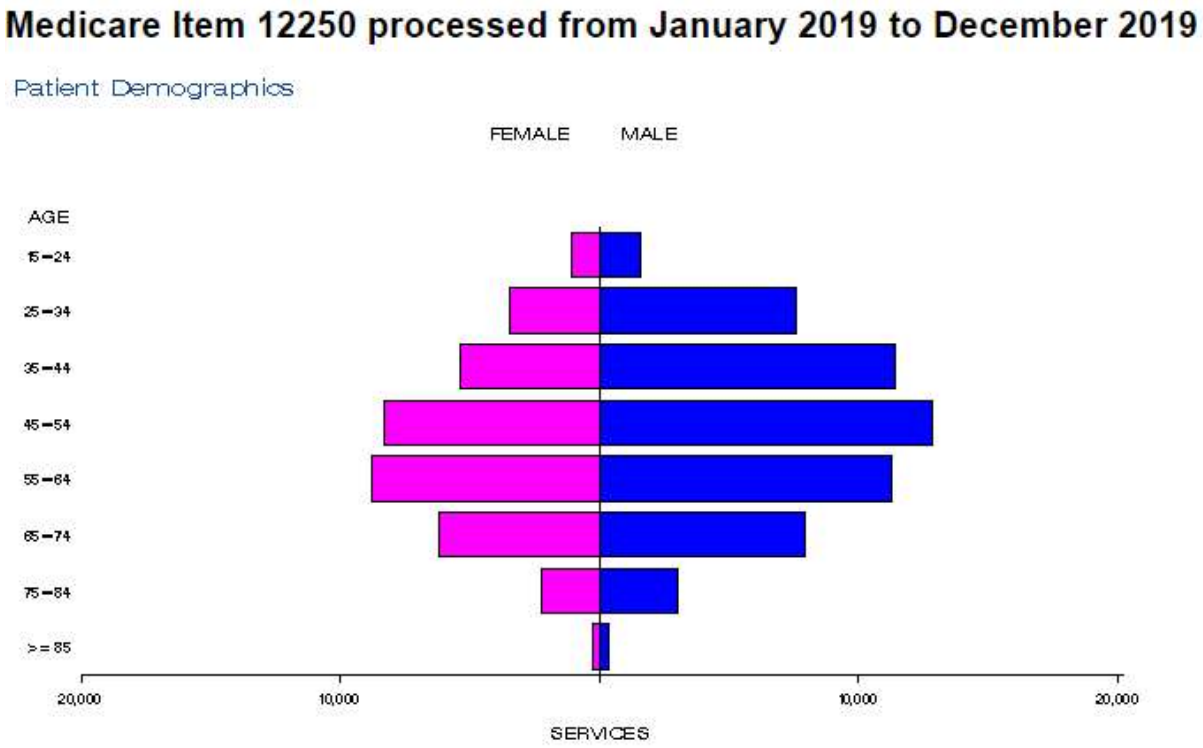
Figure 1: Utilisation MBS 12203 in 2019



MBS item 12250 is for a home sleep apnoea test and was claimed 91,763 times in 2019 and 95,967 times in 2020. Please see Figure 2 for the demographic distribution.

[6]Treager S et al *'Obstructive sleep apnea and risk of motor vehicle crash: systemic review and meta-analysis'* J Clin Sleep Med 2009 Dec 15;5 (6): 573-81.

Figure 2: Utilisation MBS 12250 in 2019



Patients are likely to initially present to a general practitioner (GP) with one or more of a variety of symptoms. These may include excessive daytime sleepiness, loud snoring, observed episodes of stopped breathing during sleep, abrupt waking with gasping or choking, waking with a dry mouth or sore throat, morning headache, difficulty in concentration, mood changes or depression or irritability, night-time sweating or decreased libido. The patient may then be referred to a sleep specialist or otherwise a GP may make a referral directly for a diagnostic sleep study when validated screening questionnaires suggest a high pre-test probability for diagnosis of moderate to severe OSA.

The patient is then likely to undergo either a Level 1 sleep investigation (12203) or a Level 2 investigation (12250). Should the result of the investigation determine that the patient has OSA, then a trial of CPAP is instigated. Should the trial of CPAP be unsuccessful in eliminating OSA, or the patient is unable to tolerate CPAP, due to claustrophobia or similar reason, a patient may be considered for UAS. In milder cases of OSA, a mandibular advancement splint (MAS) may be trialled and may be more acceptable for some patients.

Prior to surgery, an endoscopy under sedation must be performed so that the patient's upper airway anatomy may be observed in a sleep like state. The otalaryngologist is looking for the absence of a complete concentric collapse at the level of the soft palate. Patients with a complete collapse of the soft palate are not suitable for USA.

MSAC expressed concern in the PSD for application 1595 that DISE was not a commonly used procedure in Australia. The applicant intends to more thoroughly describe the current use of DISE in Australia and will incorporate this in any re-submission.

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):

As noted above patients who would be considered eligible for closed loop UAS with the Inspire® therapy would be likely to present to a General Practitioner. The patient may then be referred to a sleep physician or may proceed directly to a Level 1 or Level 2 sleep investigation. Following a diagnosis of moderate to severe sleep apnoea, a patient would undergo a trial of CPAP. Some patients with moderate OSA may trial using an MAS. Should CPAP and/or an MAS be unsuccessful or not tolerated, a patient may be considered for Closed Loop UAS. A drug induced sleep endoscopy (DISE) is conducted to exclude patients who may have a complete concentric collapse of the soft palate. Once suitability for Closed Loop UAS is confirmed a patient may proceed to implant of the Inspire® device.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The Inspire® System consists of three components, an implantable pulse generator (IPG), a respiratory sensing lead and a stimulation lead. The leads connect to the IPG via two connection ports. Please see Figure 1

Figure 1: Inspire IPG and Connector Ports

The respiratory sensing lead detects respiratory effort. The lead has a pressure-sensitive membrane that converts the mechanical energy of respiration into an electronic signal. The stimulation lead delivers stimulation to the hypoglossal nerve via a self-sizing cuff electrode that encircles the median division of the nerve. Please see Figures 2 and 3

Figure 2: Respiratory Sensing Lead

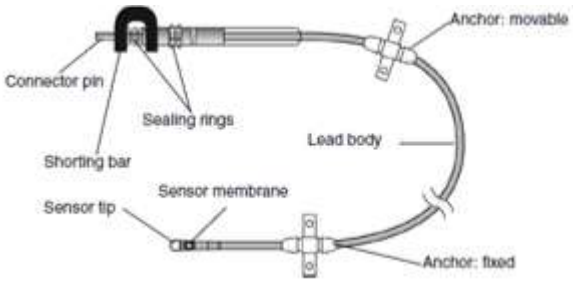
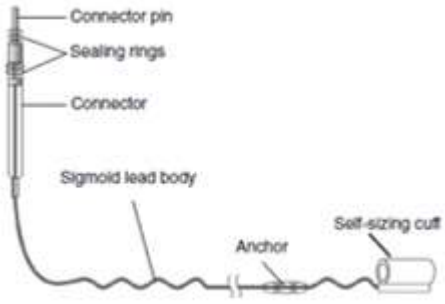
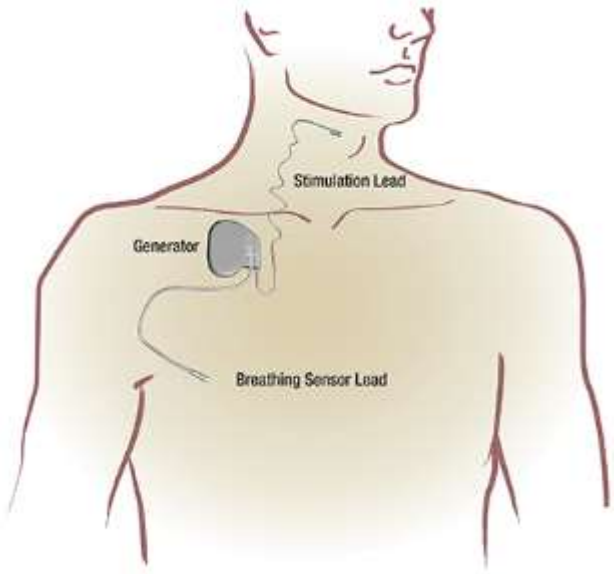


Figure 3: Stimulation Lead



The Inspire system is implanted under general anaesthetic via three small incisions. The stimulation electrode is placed on the median division of the hypoglossal nerve to recruit the tongue protrusion function. The sensing lead is placed via an incision in the fifth intercostal space and placed between the internal and external intercostal muscles to detect ventilatory effort. The IPG is place in the right ipsilateral mid-infra-clavicular region. Please see Figure 4

Figure 4: Inspire System in situ



To allow for healing, activating the device is delayed until approximately one month after surgery. The device is switched on and the patient begins therapy. The Inspire device continuously monitors the patient's breathing patterns and delivers mild hypoglossal nerve stimulation during inspiration to prevent airways collapse. The device is activated by the patient using a hand-held remote control. Therapy is adjusted by the specialist at a follow up monitoring visit(s). Patients are likely to have at least one sleep study following the procedure.

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

Yes. The device has a trademark, and the algorithm is protected by patents.

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 Inspire® Upper Airway Stimulation 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. While OSA is associated with a high BMI, the majority of clinical evidence pertains to

patients with a BMI < 32 kg/m². There is also evidence from the ADHERE Registry that demonstrates a lower BMI is a predictor of a more favourable AHI response[7]

MSAC expressed a concern that the lower AHI limit of eligible patients was not supported by the STAR trial. The applicant will further discuss the inclusion criteria by examining the baseline characteristics of the ADHERE Registry as well of those of the STAR Trial.

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

There may be limitations in access to qualified specialists who have trained in the proper use and surgical procedure associated with Inspire® therapy. Should the new medical service be recommended, and the Inspire® System subsequently included on the Prostheses List, then it is more likely that the procedure would be carried out in private hospitals on those patients who have private health insurance. There may be budget constraints in the public hospital system.

A majority of ENTs practice in major cities so patients who live in rural or remote areas may have difficulty in accessing the service.

The device battery is conservatively estimated to last 10 years, so the initial procedure is likely to be carried out only once. Once the battery has depleted, the IPG may be removed and attached to the existing leads which would remain in situ.

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

Other than the procedure to implant the device and the services associated with the hospital admission, there are no other services required.

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

Ear, nose and throat surgeon

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

The procedure cannot be delegated.

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 not anticipated that there be any limitations on who might provide a referral for a service, although it is likely that GPs, specialist sleep physicians, or respiratory physicians may be the most likely referrers. Many ear nose and throat surgeons specialise in sleep disorders.

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:

Nose and Throat surgeons will have fulfilled the requirements of the Australian Society of Otolaryngology Head and Neck Surgery (ASOHNS) or be otherwise qualified to practice this specialty in Australia.

Extensive training, provided by Inspire® Medical Systems, is required before ENTs may deliver this therapy. Training includes off-site classroom training and cadaver training. The first 3-5 cases conducted by an ENT are proctored and Inspire® Medical Systems is likely to provide continued theatre support for ENTs.

In addition to specific surgical training for ENTs, training is provided to operating room staff, sleep physicians and sleep laboratory staff. Additional training is provided to sleep physicians and other sleep or ENT clinic staff so that activation and programming of the device is appropriate.

[7] Thaler E et al *'Results of the ADHERE Upper Airway Stimulation Registry and Predictors of Therapy Efficacy'* The Laryngoscope , 130:1333-1338,2020.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> 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:

The service must be performed in an appropriate operating theatre under general anaesthetic. A proportion of patients may be appropriate for a same day discharge where others may have an overnight stay.

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

- ☒ Yes
- ☐ No

<u>PART 6c – INFORMATION ABOUT THE COMPARATOR(S)</u>

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):

The original application nominated conservative medical management as the comparator. Following considerable consultation and subsequent published real-world studies, we have determined that 'usual care' is a more appropriate comparator. Patients who are intolerant of CPAP and are suitable for UAS are unlikely to receive any active intervention. Mehra et al 2020[8] noted that of patients denied insurance coverage for UAS, 86% did not pursue any further therapy. 7% re-attempted CPAP and 3% were using an oral appliance, 3% underwent additional OSA surgery and 1% used CPAP and an oral appliance.

Altering the comparator should not otherwise change the structure of the current PICO and the availability of real-world data will enable a more accurate analysis of the costs and consequences of usual care.

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

[8] Mehra R et al *'Upper Airway Stimulation versus Untreated Comparators in Positive Airway Pressure Treatment Refractory Obstructive Sleep Apnoea.'* ANNALSATS July 14, 2020 as 10.1513/AnnalsATS.202001-015OC

The small number of patients who may pursue upper airways surgery may claim for MBS services under the following item numbers. Of these, only MBS 41786 is likely to be claimed exclusively for the treatment of OSA. Use of an MAS or CPAP are not included on the MBS.

Table 1: MBS Item 41786: Uvulopalatopharyngoplasty

Category 3 – Therapeutic Procedures
41786 UVULOPALATOPHARYNGOPLASTY, with or without tonsillectomy, by any means Multiple Operation Rule (Anaes.) (Assist.) Fee: $748.80 Benefit: 75% = $561.60

Table 2: MBS Item 30272: Partial excision of the tongue

Category 3 – Therapeutic Procedures
30272 TONGUE, partial excision of Multiple Operation Rule (Anaes.) (Assist.) Fee: $300.45 Benefit: 75% = $225.35 85% = $255.40

Table 3: MBS Item 41779: Pharyngotomy

Category 3 – Therapeutic Procedures
41779 PHARYNGOTOMY (lateral), with or without total excision of tongue Multiple Operation Rule (Anaes.) (Assist.) Fee: $712.50 Benefit: 75% = $534.40

Table 4: MBS Item 41787: Uvulectomy and Partial Palatectomy

Category 3 – Therapeutic procedures
41787 UVULECTOMY AND PARTIAL PALATECTOMY WITH LASER INCISION OF THE PALATE, with or without tonsillectomy, 1 or more stages, including any revision procedures within 12 months. Multiple Operation Rule (Anaes.) (Assist.) Fee: $577.75 Benefit: 75% = $433.35 85% = $493.05

Table 5: MBS Item 45726: Osteotomy or osteectomy

Category 3 – Therapeutic Procedures
45726 MANDIBLE OR MAXILLA, bilateral osteotomy or osteectomy of, including transposition of nerves and vessels and bone grafts taken from the same site, and excluding services to which item 47933 or 47936 apply**.** Multiple Operation Rule (Anaes.) (Assist.) Fee: $1,251.75 Benefit: 75% = $938.85

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):

As noted in Question 38, most patients will receive no further therapy. A small percentage may re-attempt CPAP, receive upper airways surgery, or trial a MAS. Please see the attached document 'Clinical Pathway Comparator'.

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:

It is difficult to estimate the number of people in the community who have failed or cannot tolerate CPAP, although the potential population is large. Should closed loop UAS be included on the MBS then a small proportion of the potential population would be able to access the therapy. Patients who have a BMI > 32, have total concentric collapse or who are aged less than 18 are not eligible.

A small number of patients who may otherwise have upper airways surgery may receive closed loop UAS instead.

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):

The pathway following implementation of Inspire® therapy is similar to that following usual care. It is however less likely that patients would use CPAP as is the case with some patients following surgery. In the STAR trial patients were classified as responders if there was a decrease in AHI > 50% and AHI < 20, however most patients who were not classified as responders still reported reductions in symptoms of OSA. It is possible that some patients might proceed to surgery, although this is likely to be fewer than in the absence of closed loop UAS and in extreme cases tracheostomy may be considered although this is considered unlikely. Non-responders would likely receive no further active intervention, or a small number may possibly reattempt CPAP and/or MAS.

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):

Inspire® therapy is superior to usual care for patients with moderate to severe OSA and who have failed or unable to tolerate CPAP.

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)

Oxygen Desaturation Index (ODI)

Quality of Life – Epworth Sleepiness Scale (ESS)

- Functional Outcomes of Sleep Questionnaire (FOSQ)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

As noted in Question 24 the Sleep Health Survey of Australian Adults estimated that the prevalence of doctor diagnosed sleep apnoea is 8.3% overall. As CPAP therapy does not have an MBS item number, or its use otherwise recorded in a publicly available source, it is very difficult to determine the number of patients in Australia currently being treated by CPAP and hence difficult to calculate how many may have failed CPAP therapy.

A useful alternative approach may be to look at the number of sleep studies conducted in Australia and use these numbers to estimate a population. A total of 135,148 primary diagnostic sleep studies (MBS items 12203 and 12250) were conducted in 2019. There is also no publicly available data that records how many sleep studies result in a diagnosis of moderate to severe OSA. In the absence of publicly available data that reports the outcomes of sleep studies in Australia, we have used Escourrou et al 2015[9], to determine the number of patients likely to be diagnosed with moderate to severe OSA. Escourrou et al presented data from 11,049 patients in the multi-centre European Sleep Apnoea Cohort (ESADA) with suspected OSA (male and female, aged 18-80 years.) There were 5,304 patients with PSG data to evaluate OSA outcomes. 24% of the cohort had moderate OSA and 41% had severe OSA. Assuming 65% of the patients receiving a primary sleep study in Australia are diagnosed with moderate to severe OSA then there are likely to be **87,846** new cases each year.

The Australasian Sleep Association[10] estimates that approximately 50% of patients are likely to fail or be non-adherent to CPAP. Therefore, there are likely to be **43,923** who may be considered for UAS. The original PICO population defined the population as those over 18 who have a BMI > 32kg/m². An Australian study of 163 consecutive sleep studies of patients who did not previously have a diagnosis of OSA analysed BMI data of those patients[11]. Please see the graph reproduced in Figure 3. Extrapolating from the graph, 41 (45.1%) of the 91 patients diagnosed with moderate to severe OSA had a BMI < 30 kg/m². Therefore **19,811** patients are likely to be eligible. To account for the discrepancy between a BMI < 32 and the study classification of BMI < 30, it is assumed that an additional 10% of patients will be eligible resulting in an eligible population of

Not all patients who are referred receive closed loop UAS, 8% are likely to be excluded due to complete concentric collapse identified at DISE[12] leaving an eligible population of **20,048.**

These calculations are summarised in Table 6.

[9] Escourrou, P. *et al.* The diagnostic method has a strong influence on classification of obstructive sleep apnea. *J Sleep Res* **24**, 730-738, doi:10.1111/jsr.12318 (2015).

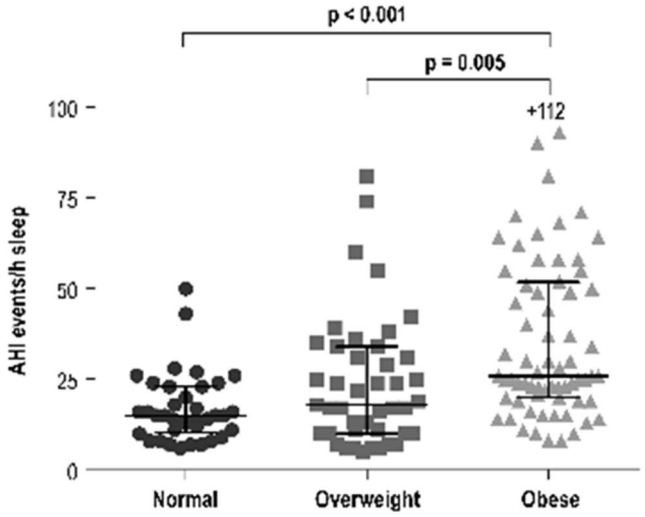
[10] Australasian Sleep Association *'Australasian Sleep Association submission re: Adult Sleep Apnea Surgery'* 2013. https://sleep.org.au/common/Uploaded%20files/Public%20Files/Professional%20resources/Sleep%20Documents/ENT%20MSAC.pdf

[11] Gray et al *'Obstructive Sleep Apnea without Obesity Is Common and Difficult to Treat: Evidence for a Distinct Pathophysiological Phenotype'* J Clin Sleep Med. 2017; 13 (1): 81-88

[12] Strollo PK et al 'Upper-Airway Stimulation for Obstructive Sleep Apnea' N Engl J Med 2014; 370:139-49

Figure 3: Excerpt from Gray et al 2015

Figure 1—Distribution of obstructive sleep apnea severity by body mass index category.



AHI = apnea-hypopnea index measured via overnight in-laboratory polysomnography. Data are shown as individual participant values plus median and interquartile range. Note: "+112" refers to a single patient who had an AHI of 112 events/h of sleep.

Table 6

Description	Source	Estimated Population
Annual Sleep Studies	**MBS items 12203 and 12250**	**135,148**
65% with diagnosis of moderate to severe OSA	**Escourrou et al 2015**	**87,846**
50% failure of CPAP	**Australasian Sleep Association**	**43,923**
45.1% BMI < 30	**Gray et al 2017**	**19,809**
10% adjustment for patients with BMI ≥ 30 < 32	**Assumption**	**21,790**
Exclude 8% of patients with complete concentric collapse	**Strollo et al 2014**	**20,047**

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

Once

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

One. It is conservatively anticipated that the IPG would be replaced after 10 years.

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

While the eligible population for closed loop USA is large, there are considerable restraints within the Australian health care system, similar to other jurisdictions, which makes it likely that a limited population is likely to access the service. The service is only suitable for implementation in centres which are able to integrate the surgical and sleep medicine teams. The applicants experience in western Europe and the Unites States has been that tertiary teaching hospitals are the most suitable for delivering the service.

There are significant training requirements that must be met, prior to the implementation of the service. These include individual cadaver training for each surgeon and considerable proctoring for the initial cases conducted by each surgeon. Another constraint is the number of ENTs in Australia. In 2016 there were 460 ENTs in Australia[13]. Each centre would be likely to be able to carry out 8 – 10 procedures in the first year of operation. The applicant estimates that should the service be recommended for funding, that three centres would likely be operational in the first year, with an estimated utilisation of 8-10 cases per year.

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:

Noting the restraints outlined in Question 49, there are additional constraints including the capacity of the hospital system to absorb the additional procedures and the rate of diffusion of the technology. MSAC expressed concern in PSD 1595 that the utilisation may be significantly higher than estimated in the ADAR**. REDACTED**.

The estimated number of procedures for the first 5 years is taken from ADAR 1595 and reproduced in Table 7.

Table 7: Estimated centres and utilisation for Australia

Year	Estimated number of centres	Estimated number of patients	Estimated Utilisation
Year 1	3	8	24
Year 2	5	8	40
Year 3	7	8	56
Year 4	10	10	100
Year 5	15	10	150

Additionally, the applicant would like to propose the use of an item number for a case conference to determine eligibility for closed loop UAS, similar to those currently available for transcatheter aortic valve implantation (TAVI) (MBS items 6080 and 6081). At a minimum, the team would include an ear, nose and throat surgeon and a sleep specialist.

[13] Australian Department of Health, Otolaryngology 2016 Fact Sheet

PART 8 – COST INFORMATION

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

Table 8: Costs of Closed Loop UAS

Service	Source	Fee/Cost	Benefit	Frequency	Cost
Presurgical services					
DISE	MBS Item 41764	$124.80	$93.60	1	$106.10
	MBS Item 41889	$180.90	$135.70	1	$135.70
Case Conference - Coordination	Proposed Fee	$52.50	$44.65	1	$89.30
Attendance Case Conference	Proposed Fee	$39.15	$33.30	2	$66.60
Surgical Services					
Subcutaneous Placement of IPG	Proposed Fee	$346.05	$259.55	1	$259.55
Implantation of hypoglossal nerve lead	Proposed Fee	$684.95	$513.75	1	$513.75
Implantation of respiratory sensing lead	Proposed Fee	$684.95	$513.65	1	$513.65
Surgical repositioning or removal of IPG	Proposed Fee	$161.95	$121.50	0.016	$1.95
Anaesthesia	MBS Item 20320	$120.60	$90.45	1	$90.45
	MBS Item 23091	$180.90	$135.70	1	$135.70
Post-op Chest x-ray	MBS Item 58500	$35.35	$26.55	1	$26.55
Post-op neck x-ray	MBS 57945	$43.40	$32.85	1	$32.85
Hospitalisation	AR-DRG D12B	$4,778	$4,778	1	$4,778
Follow up					
Programming Inspire Device	MBS 105	$44.35	$37.70	2	$75.40
DISE	MBS Item 41764	$124.80	$93.60	1	$106.10

The Inspire Upper Airways Stimulation System including IPG, stimulation lead, respiratory sensing lead and sleep remote is **REDACTED**.

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

The surgery takes approximately 2 hours to perform.

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.

Category 1 PROFESSIONAL ATTENDANCES
XXXX Coordination of a Closed Loop UAS Case Conference by a Closed Loop Upper Airways Stimulation (UAS) practitioner where the Closed Loop UAS Case Conference has a duration of 10 minutes or more.
Fee: $52.50 Benefit: 75% = $39.40 85% = $44.65

Category 1 PROFESSIONAL ATTENDANCES
XXXX Attendance at a Closed Loop UAS Case Conference by a specialist or consultant physician who does not also perform the service described in XXXX for the same Case Conference where the Closed Loop UAS Case Conference has a duration of 10 minutes or more.
Fee: $39.15 Benefit: 75% = $29.40 85% = $33.30

Category 3 – THERAPEUTIC PROCEDURES
XXXX Unilateral closed-loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, including: i) subcutaneous placement of electrical pulse generator, ii) surgical placement of lead including connection of the lead to the hypoglossal nerve and intra-operative test stimulation iii) surgical placement of respiratory lead and intra-operative test stimulation for management of moderate to severe obstructive sleep apnoea in a patient who: a) has an Apnoea Hypopnoea Index of greater than or equal to 15 and less than or equal to 65; and b) is aged 18 and over; and c) has failed or is intolerant to continuous positive airway pressure or bilevel airway pressure; and d) has a BMI less than or equal to 32 kg/m²; and e) does not have complete concentric collapse of the upper airway Only once per patient Multiple Operation Rule (Anaes.)
MBS Fee: $943.00 Benefit 75% = $707.25 (in-hospital/admitted patient only)

MSAC expressed concern that there might be additional costs due to the use of an assistant surgeon. There is no procedural reason that an assistant surgeon would need to participate in the surgery.

Category 3 – THERAPEUTIC PROCEDURES
MBS item XXXX Unilateral closed-loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, surgical repositioning or removal of electrical pulse generator for management of moderate to severe obstructive sleep apnoea ~~in~~ Only once per patient Multiple Operation Rule (Anaes.)
MBS Fee: $161.95 Benefit 75% = $121.50 (in-hospital/admitted patient only)

MSAC expressed concern that there might be additional costs due to the use of an assistant surgeon. There is no procedural reason that an assistant surgeon would need to participate in the surgery.

Category 3 – THERAPEUTIC PROCEDURES
MBS item XXXX Unilateral closed loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, surgical replacement of electrical pulse generator Multiple Operation Rule
MBS Fee: $346.05 Benefit 75% = $259.55 (in-hospital/admitted patient only)

MSAC expressed concern that there might be additional costs due to the use of an assistant surgeon. There is no procedural reason that an assistant surgeon would need to participate in the surgery.