

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1595.1 – Closed loop upper airway stimulation for moderate to severe obstructive sleep apnoea, in patients who have failed or are intolerant to, continuous positive airway pressure therapy

Applicant: Inspire Medical Systems Inc.

Date of MSAC consideration: 30-31 March 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#).

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing, with a subsequent request for listing on the Prostheses List (PL), of closed loop upper airway stimulation (UAS) for the treatment of moderate to severe sleep apnoea (OSA) in patients who have failed or are intolerant of continuous positive airway pressure (CPAP) was received from Inspire Medical Systems Inc. by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support the creation of new Medicare Benefits Schedule (MBS) items for closed loop upper airway stimulation (UAS) for moderate to severe obstructive sleep apnoea (OSA) in patients who have failed, or are intolerant to, continuous positive airway pressure (CPAP) therapy. MSAC considered that the primary evidence base for the treatment was unchanged from MSAC's previous consideration in November 2020, had a high risk of bias, and it was uncertain whether better evidence is currently available. MSAC considered the available evidence indicated inferior safety outcomes for UAS relative to no active treatment. Benefits in terms of effectiveness were uncertain, with some improvements in surrogate outcomes but no evidence of benefit for cardiovascular outcomes. MSAC considered that the inadequacy of the evidence base, particularly on cardiovascular outcomes, affected the robustness of the economic modelling and hence the reported ICER. MSAC considered that the size of the population likely to qualify for this procedure under the proposed item descriptors remained uncertain, as OSA is a highly prevalent condition, and failure or intolerance of CPAP is common. As a result, the subpopulation needs to be better defined. MSAC considered that this risk of "leakage" also affected the robustness of the estimates of the financial costs of listing. MSAC considered that the cost of the proposed item needs to be better justified, including the role of drug-induced sleep endoscopy (DISE) and out-of-pocket costs for patients.

Consumer summary

This is an application from Inspire Medical Systems requesting Medicare Benefits Schedule (MBS) listing of closed loop upper airway stimulation for moderate to severe obstructive sleep apnoea, in patients who have failed or are intolerant to, continuous positive airway pressure therapy (often referred to as CPAP therapy).

Obstructive sleep apnoea is a sleep disorder where a person's upper airway becomes completely or partially blocked during sleep. "Apnoea" is when breathing stops for 10 seconds or more. In moderate to severe sleep apnoea, people have between 15 and 65 episodes of airway blockage every hour, which leads to poor sleep.

Closed loop upper airway stimulation aims to send electrical signals to a person's hypoglossal nerve when they are asleep. The hypoglossal nerve controls muscles in the upper airway (throat) and tongue. Sending electrical signals to the nerve affects the muscles, which allows the airway to open and the person to breathe normally. The upper airway stimulation system is a device that has to be inserted during surgery. It has an electrical lead that senses the person's breathing while they sleep. When breathing stops, the device sends a mild electrical signal through another electrical lead to the hypoglossal nerve, which stimulates the nerve and opens the airways.

MSAC felt that the evidence in the application did not sufficiently establish the long-term safety of closed loop upper airway stimulation. MSAC also felt that although the evidence showed that closed loop upper airway stimulation led to some improvements in patient reported outcomes it was unable to satisfactorily demonstrate concrete improvements in health (e.g. blood pressure, heart attack and stroke rates). MSAC was also concerned that the patient group that would be eligible for treatment with upper airway stimulation was not defined well enough and this might lead to additional people who are not eligible also getting the service since obstructive sleep apnoea is a very common condition.

MSAC also felt there were some issues with the economic model that made it very uncertain if upper airway stimulation would be good value for money.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support MBS funding for closed loop upper airway stimulation for people with moderate to severe obstructive sleep apnoea. This is because MSAC was not convinced that upper airway stimulation was safe and effective for everyone, and was uncertain if it would be good value for money.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was a resubmission to request Medicare Benefits Schedule (MBS) listing of closed loop upper airway stimulation (UAS) for moderate to severe obstructive sleep apnoea (OSA), in patients who have failed or are intolerant to, continuous positive airway pressure (CPAP) therapy. The previous submission had been considered by [MSAC in November 2020](#), and MSAC had not recommended MBS funding. MSAC's requirements for a resubmission are shown in Table 1.

Table 1 Requirements for a resubmission for application 1595

Item	MSAC advice
Use of DISE as a prior test	Address the uncertainty regarding the use of DISE as raised by ESC
Population and clinical place	There may be a subpopulation of patients who have failed all other medical management options where UAS therapy may be appropriate. The resubmission would need to define this subpopulation using the appropriate eligibility criteria.
Clinical evidence	Provide evidence to support use of UAS in this refined population
Economic evaluation	Improve the economic model to address the uncertainties regarding the model structure, time horizon (and device replacement due to end battery life), effect size (AHI/mortality) estimate as raised by ESC. The resubmission should also reduce the cost of the device in order to ensure cost-effectiveness
Financial estimates	Update, as required (see above)

Abbreviations: AHI=apnoea hypopnoea index; DISE=drug induced sleep endoscopy; UAS=upper airway stimulation

Source: [Public Summary Document for application 1595, page 4](#)

MSAC noted that the proposed item descriptor had been updated to define “failed or intolerant to CPAP therapy”, as requested by PASC. The updated item descriptor specified that this treatment was suitable for “(i) patients who have failed CPAP where CPAP failure is defined as continued apnoea hypopnoea index (AHI) > 20 despite appropriate CPAP usage, or (ii) who are intolerant of CPAP where CPAP intolerance is defined as inability to use CPAP (>5 nights per week of usage: usage defined as >4 hours of use per night) or unwillingness to use CPAP, or (iii) patients who are unsuitable for, or have unsuccessfully attempted all other appropriate interventions and who are currently untreated”. MSAC considered that it was still unclear from this revised description what the reference to ‘all other appropriate interventions’ specifically referred to (e.g. do all these patients have to undergo surgery and what if they choose not to?). MSAC also considered that the item descriptor made use of an excessive number of ‘or’ conditions (as described above). The use of the term ‘unwillingness to use CPAP’ may be too subjective and open-ended, creating a risk of leakage under the proposed item descriptor given that OSA is a highly prevalent condition. MSAC noted that the terms “no active treatment”, “adjunctive therapy” and “mainstay therapy” were used interchangeably throughout the application, leading to a lack of clarity regarding the proposed population.

MSAC considered that these issues meant that even though in its pre-MSAC response the applicant indicated that it was willing to further amend its item descriptor as originally requested by PASC, further clarity was required regarding the terms “intolerant” of CPAP and ‘unwillingness to use CPAP’.

MSAC noted while the applicant’s pre-MSAC response had addressed many of the issues raised by ESC, other issues which remained outstanding and had not been adequately addressed were:

- The use of drug induced sleep endoscope (DISE) as a prior test. While the applicant had confirmed that DISE should be mandatory before undergoing UAS, MSAC again noted that DISE is not commonly performed in Australia and were unconvinced about the clinical need, place and provision of this procedure as part of the proposed clinical algorithm for upper airway stimulation.
- The proposed cost of the device – MSAC considered that this should be aligned with the cost of similar devices for vagus nerve stimulation. Because both UAS and vagus nerve stimulators are neuromodulators, MSAC expected that these devices would be in the same subcategory of the Prostheses List (PL) and therefore have comparable costs.
- Out-of-pocket costs for patients – MSAC considered that out-of-pocket costs would be substantial if the device was not listed on the PL and that there were also uncertainties about potential out of pocket costs associated with the use of DISE (which the applicant has confirmed should be mandatory).

MSAC noted the issues with the clinical evidence base and literature review that were identified by ESC and the commentary; in particular, that more recent studies had not been integrated into the resubmission, and studies included in the ADAR did not align with the PICO criteria and did not include a risk of bias assessment. MSAC also noted that while the commentary had identified other studies, many were industry sponsored and at high risk of bias.

MSAC agreed with the concerns raised by ESC that there was no data on long term comparative safety identified in the ADAR. MSAC considered that the procedure presented a low risk, but noted the significant side effects from the intervention, such as discomfort due to electrical stimulation (reported by 40–60% of patients) and tongue abrasion (reported by 27% of patients). MSAC therefore considered that UAS had inferior safety to the comparator.

MSAC agreed with the concerns raised by ESC and the commentary regarding comparative clinical effectiveness. MSAC considered that the clinical claim of superior effectiveness may be supported for surrogate outcomes (AHI, oxygen desaturation threshold index, quality of life), but was not supported for cardiovascular outcomes based on blood pressure endpoints, and there is no evidence of superior effectiveness for long-term health outcomes.

MSAC noted the economic evaluation and agreed with the concerns raised by ESC and the commentary. The model was particularly sensitive to changes in the time horizon. The base case ICER using a lifetime time horizon (\$47,662) increased to \$63,899 using a 15-year time horizon, and \$113,845 using a 5-year time horizon. MSAC noted that the model was also sensitive to assumptions on utility gains and whether changes in surrogate outcomes translated into changes in cardiovascular outcomes. Regarding utility gains, MSAC noted that the model assumed that UAS-treated patients would achieve the same health related quality of life (HRQoL) as patients treated with CPAP. This assumption was based on the STAR trial's findings on improvements in values for the Epworth Sleepiness Scale (ESS) and the Functional Outcomes on Sleep Questionnaire (FOSQ) and was extremely favourable to the intervention (e.g. reducing the gain in HRQoL to 50% increases the ICER to \$73,565/QALY gained). Regarding changes in surrogate outcomes, MSAC noted that the model assumed that a reduction in AHI would lead to a reduction in cardiovascular risk. However, if no reduction in cardiovascular risk from UAS is assumed, this increases the ICER to \$76,340/QALY gained.

MSAC noted that the applicant had reduced the cost of the device by 16.7%; however, this cost was still higher than the cost of the comparable device for vagus nerve stimulation. MSAC noted that aligning the cost of UAS with the cost of vagus nerve stimulation, over a 15-year time horizon, reduced the ICER to \$35,867.

MSAC considered that the key uncertainties in the economic model were

- The use of a lifetime time horizon. A shorter time horizon would significantly increase the ICER as noted above but the applicant's pre-MSAC response contended that if a shorter (15 year) time horizon was used this would bias the results unfavourably against UAS if the assumption that devices needed battery replacement every 11 years was retained.
- The assumptions that the effectiveness of UAS was maintained over a patient's lifetime while there were no improvements in health in the comparator arm. In addition that improvements in surrogate outcomes from UAS would translate into improvements in cardiovascular outcomes were unsupported by the published literature.
- The economic model did not account for non-responders (15% of patients in the STAR trial).

MSAC noted the financial and budgetary impacts, and agreed with the concerns raised by ESC and the commentary. MSAC noted that access to UAS would be severely limited based on the capacity of centres and trained surgeons to perform the procedure, which raises equity issues.

MSAC noted that the commentary had estimated the total cost to the MBS over 6 years as \$1,334,488, and the cost to the PL would be up to \$6,096,000.

MSAC noted that there was no information about the outcomes that patients value from UAS and how any benefits compare to any safety issues they experience. Although this would be accounted for in the quality of life estimates using the ESS, MSAC considered that this could be addressed with a more clearly defined patient population in which the potential benefits might outweigh the inferior safety aspects of UAS.

MSAC clarified the following queries from the department:

- If MBS funding of UAS were supported,
 - an item should be included specifically for replacement of the battery in the device (to align with items for vagus nerve stimulation) to allow for tracking of battery life
 - an item should be included for repositioning or removal of the leads (to align with vagus nerve stimulation item 40705 for repositioning or removal of the lead)
 - surgical assistance (implantation) is required, but it remained unclear whether anaesthesia is required for device replacement
 - the device implantation item should be restricted to once per lifetime (but other items do not require this restriction)
 - selected co-claiming restrictions are required
 - the procedure would be a Type B procedure
 - The required expertise and management with a multidisciplinary environment should be addressed in the item descriptor

MSAC considered that any potential resubmission for UAS should address the following:

- safety – address the uncertainties regarding long-term safety.
- effectiveness – ensure the evidence base is complete and up to date, provide clarity regarding the use of DISE as a prior test in the Australian context, and clearly identify a subpopulation of patients for whom UAS might be appropriate.
- cost-effectiveness – address uncertainties regarding the time horizon, device/battery replacement, non-responders, DISE costs and out-of-pocket costs for patients.
- financial and budgetary impact – align the device cost with other devices in the same subcategory on the PL (such as vagus nerve stimulation), and address uncertainties regarding the risk of leakage to a broader population.
- item descriptor – further clarify the eligible population to minimise the risk of leakage.

4. Background

This is a resubmission, an applicant developed assessment report (ADAR) for closed loop UAS for the treatment of moderate to severe OSA was considered by MSAC in November 2020 (Application 1595). MSAC did not recommend publicly funding closed loop UAS.

MSAC Application 1630 is for hypoglossal nerve stimulation using the Geno System for the treatment of moderate to severe OSA in patients who have failed or are intolerant to CPAP. The application is expedited, bypassing PASC. A third system, LivaNova THN Sleep Therapy system is currently in clinical trials. Although these systems are both UAS systems, neither are ‘closed loop’ defined by the respiratory sensing lead.

The PICO Confirmation for MSAC application 1595.1 was considered by the PICO Confirmation Advisory Sub-Committee (PASC) at their meeting in August 2021. Key issues raised by MSAC and the Evaluation Sub-Committee (ESC), following the assessment of Application 1595, and those raised by PASC considering the resubmission are outlined in Table 2.

Table 2 Summary of key matters of concern

Component	Matter of concern	How the current assessment report addresses it
Item descriptor	<p>ESC considered that for the MBS item descriptor:</p> <ul style="list-style-type: none"> • CPAP failure and lack of tolerance to CPAP should be defined. • Once per lifetime per patient was appropriate for surgical repositioning or removal of the device, but not for replacement of the device. • Unnecessary patient descriptions should be removed from the descriptors for repositioning or removal, and replacement. (PSD, p.24). <p>PASC requested:</p> <ul style="list-style-type: none"> • That surgical repositioning or removal be only once per lifetime, instead of once per patient as stated in the proposed item descriptor. (PICO Confirmation, p.17). • The addition of an MBS explanatory note that identified the required expertise and management within a multidisciplinary environment (PICO Confirmation, p.18). 	<p>Not adequately addressed</p> <p>The ESC requests are addressed in a revised item descriptor approved by PASC.</p> <p>The change to 'once per lifetime' has been made.</p> <p>An explanatory note has not been included or discussed.</p>
Use of DISE as a prior test	<p>p24 of the PSD: ESC noted that DISE is not a well described test, and current funding for, and utilisation of, DISE are uncertain.</p> <p>Table 1 of the PSD: MSAC advised that the uncertainty regarding the use of DISE as raised by ESC should be addressed in a resubmission.</p>	<p>Not adequately addressed</p> <p>The ADAR describes scenarios where DISE is used but they are not referenced, and no source is acknowledged. However the applicant's pre-ESC response notes that the ADAR has referenced the Australasian Sleep Association position statement on surgical management which lists sleep nasoendoscopy as an optional investigation of OSA.</p> <p>The ADAR does not provide any additional information on the current and proposed role of DISE although it is included in the clinical algorithm.</p>

Component	Matter of concern	How the current assessment report addresses it
Population and clinical place	Table 1 of the PSD: MSAC advised there may be a subpopulation of patients who have failed all other medical management options where UAS therapy may be appropriate. The resubmission would need to define this subpopulation using the appropriate eligibility criteria.	Not adequately addressed. No active treatment or care remains poorly defined. In particular, the role of upper airway surgery is not described and not included in the clinical management algorithms. A specific subpopulation of patients who have failed other options and is eligible for UAS has not been clearly defined.
Clinical evidence	p1 of the PSD: MSAC considered that the evidence did not demonstrate that the safety and effectiveness of UAS in the proposed MBS population had been established. Table 1 of the PSD: The resubmission was required to provide evidence to support the use of UAS in a subpopulation of patients who have failed all other medical management options and where UAS therapy may be appropriate.	Not adequately addressed. The resubmission has re-presented evidence from Application 1595 and not synthesised it with new studies. It relies on the STAR study ¹ which was the basis of Application 1595. A single study that compares UAS with no active care (Mehra, 2020 ²) was identified but not used in the clinical evaluation. The PICO Confirmation noted 'there are two new randomised trials that will be available in 2021.' The EFFECT trial ³ has recently been published and it is anticipated that the CARDIOSA-12 trial is likely to be published later this year, which will be used to support superiority of Inspire over usual care (i.e., no active treatment). Neither trial is used to support the clinical claim. The clinical evidence has not been adequately presented in the ADAR.
Economic evaluation	Table 1 of the PSD: Improve the economic model to address the uncertainties regarding the model structure, time horizon and effect size as raised by ESC. The resubmission should also reduce the cost of the device in order to ensure cost-effectiveness.	Not adequately addressed. The time horizon of the base case has not been altered in the resubmission. A more complex model has been presented; however, this does introduce further parameter uncertainty as most inputs are not taken from studies that directly relate to the specified PICO. The cost of the device has been reduced by 16.7%.

¹ Single arm: Strollo Jr PJ, et al. (2014). 'Upper-airway stimulation for obstructive sleep Apnoea', *New England Journal of Medicine*, 370(2):139-49.

Randomised sub-study: Woodson B et al. (2014). 'Randomized controlled withdrawal study of upper airway stimulation on OSA: short- and long-term effect', *Otolaryngology--head and neck surgery*, 151(5):880-7.

² Mehra R, et al. (2020). 'Upper airway stimulation versus untreated comparators in positive airway pressure treatment-refractory obstructive sleep Apnoea', *Annals of the American Thoracic Society*, 17(12):1610-9.

³ Heiser C, et al. (2021). 'Effect of upper airway stimulation in patients with obstructive sleep Apnoea (Effect): a randomized controlled crossover trial', *Journal of clinical medicine*, 10(13): 2880.

Component	Matter of concern	How the current assessment report addresses it
Financial estimates	Table 1 of the PSD: Update to address the subpopulation of patients who have failed all other medical management options.	Not adequately addressed. The estimate of number of patients treated is not altered from Application 1595 and is based on limited access rather than eligible patient population.

ADAR = Applicant Developed Assessment Report; DISE = drug-induced sleep endoscopy; ESC = Economic Sub-committee; MSAC = Medical Services Advisory Committee; PICO = Population, Intervention, Comparator, Outcome; PSD = Public Summary Document; UAS = upper airway stimulation. Source: Table 2 of MSAC Application 1595.1 adapted by the commentary, references to the PSD are to the PSD for Application 1595.

5. Prerequisites to implementation of any funding advice

The proposed service requires the provision of an active implantable device, the Inspire® System. There are five registered components of the Inspire® System, all of which are included on the Australian Register of Therapeutic Good (ARTG). Please see Table 3. The system was included on the ARTG on 6 August 2020,

Table 3: Inspire® System Components ARTG numbers

Component	ARTG Number
Inspire Sleep Remote Model 2500	340934
Inspire Physician Programmer Model 2740	340933
Inspire Respiratory Sensing Lead Model 4340	340932
Inspire Stimulation Lead Model 4063	340931
Inspire IV Implantable Pulse Generator	340930

Source: Table 3 of MSAC Application 1595.1

Should the MSAC recommend public funding for the implantation of the Inspire® System, then an application will be made to include the device on the PL.

A training program and in-theatre support for each implant for the initial 18-months is provided by the applicant.

6. Proposal for public funding

The applicant proposed the creation of new MBS item numbers for closed loop UAS. The proposed fee has been based on the item numbers for placement of a vagal nerve stimulator.

The proposed new MBS item for placement of a closed loop UAS is presented in Table 4, taken from the PICO Confirmation (the ADAR presented the proposal for Application 1595). The fee requested in the resubmission is the same as in Application 1595. It is calculated based on existing item numbers for vagal nerve stimulation:

- Item 40701 subcutaneous placement of IPG - MBS fee \$360.05
- Item 40704 placement of lead – MBS fee \$712.65 (claimed twice, once for the stimulation lead and once for the respiratory sensing lead)

These have then been combined into a single item number according to the multiple operation rule. Using current fees for these item numbers, the total proposed fee should be \$1,158.99 (40704 + 50% 40704 + 25% 40701).

Table 4 Proposed new MBS item for placement of closed loop UAS

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS item *XXXX</p> <p>Unilateral closed-loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, including:</p> <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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 of continuous positive airway pressure or bi-level 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 iv) who have failed CPAP where CPAP failure is defined as continued AHI > 20 despite appropriate CPAP usage or v) who are intolerant of CPAP where CPAP intolerance is defined as inability to use CPAP (> 5 nights per week of usage: usage defined as > 4 hours of use per night or unwillingness to use CPAP or Patients who are unsuitable for, or vi) have unsuccessfully attempted all other appropriate interventions and who are currently untreated. <p>Once per lifetime</p> <p>Multiple Operation Rule</p> <p>(Anaes.)</p>
<p>MBS Fee: \$943.00 Benefit 75% = \$707.25 (in-hospital/admitted patient only)</p> <p>MBS Fee (based on existing items): \$1,158.99 Benefit 75% = \$869.24</p>

Source: Ratified PICO Confirmation, Section 1, page 17.

Note: Assessment Group suggested amendments are shown in **blue text**.

The proposed new MBS item for repositioning or removal of the pulse generator is presented in Table 5. The commentary questions why no item has been proposed that aligns with vagal nerve stimulation item 40705 for repositioning or removal of the lead (fee \$640) and why repositioning is ‘once per lifetime.’ Safety data demonstrates that a single patient can undergo multiple repositioning procedures.

Table 5 Proposed new MBS item for repositioning or removal of the pulse generator

Category 3 – THERAPEUTIC PROCEDURES
<p>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</p> <p>Only once per lifetime</p> <p>Multiple Operation Rule</p> <p>(Anaes.)</p>
<p>MBS Fee: \$168.55 Benefit 75% = \$126.50 (in-hospital/admitted patient only)</p>

Source: ADAR, Section 1, Table 9.

The proposed new MBS item for replacement of the pulse generator is presented in Table 6. The commentary states that the proposed item should be specifically for battery replacement if it is to align with item 40708 (vagal nerve stimulation battery replacement), and not be a duplicate with the proposed item for both repositioning and replacement. This would also provide a means of tracking battery longevity to confirm it aligns with the applicant’s claims.

Table 6 Proposed new MBS item for battery replacement

Category 3 – THERAPEUTIC PROCEDURES
Unilateral closed loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, surgical replacement of <i>battery in</i> electrical pulse generator
Multiple Operation Rule
MBS Fee: \$168.55 Benefit 75% = \$126.50 (in-hospital/admitted patient only)

Source: ADAR, Section 1, Table 10.

Note: Assessment Group suggested amendments are shown in [blue text](#).

The ADAR also proposed two new MBS items for closed loop UAS case conferences. Department advice is that specific case conference items for UAS should not be created as alternative appropriate case conference items are already available on the MBS. Therefore, PASC considered that the item descriptors for UAS should specify the requirement for a case conference and that there needs to be clarification and agreement of the multidisciplinary clinical expertise required for the case conference. It was noted that multidisciplinary expertise required for the case conference could be specified in an explanatory note. The commentary notes that this advice from PASC was not addressed in the ADAR. The applicant’s pre-ESC response acknowledged this but clarified that p. 31 of the ADAR notes that at a minimum, a case conference should include a sleep physician and ear, nose and throat surgeon; and that a dentist, orthodontist and sleep psychologist may be included as appropriate.

7. Population

The population specified in the Ratified PICO Confirmation and in the ADAR is patients aged ≥ 18 years with a body mass index (BMI) < 32 kg/m² and moderate to severe OSA, defined as having an AHI ≥ 15 and ≤ 65 , and who have been confirmed to have failed or cannot tolerate CPAP therapy or bi-level positive airway pressure (BIPAP) therapy. Patients with complete concentric collapse at the soft palate level are not eligible. Patients are receiving no active treatment, have trialed or are not suitable for all other treatment options.

PASC stated that “in clinical practice UAS is a niche therapy considered as a last resort for patients after excluding more common therapies for OSA, involves multidisciplinary team assessment of individual patient eligibility including CPAP failure, which should be demonstrated in an expert centre where the proposed intervention would be appropriate.” Therefore, the proposed service would be used where no alternative technology is available. However, PASC also noted that “there may be unwillingness to undergo CPAP, and the threshold for unwillingness could be low as cost is entirely borne by patients, and the market is unchecked with care not always delivered by health practitioners.”

The ADAR fails to clearly define the subpopulation for which UAS is an appropriate therapy. It is not specified which treatments should have been attempted, what level of investigation is required to define failure of these treatments, the role of multidisciplinary assessment for

eligibility or whether there are any other prerequisites to eligibility for UAS given PASC defined it as a niche therapy.

The commentary considers that the role of upper airway surgery in the clinical algorithm is not well described in the ADAR. Upper airway surgery is a mainstream therapy for OSA but its role is not shown in the clinical management algorithms and whether UAS would substitute for upper airway surgery, or conversely increase in volume as patients pursue surgery in order to access UAS, is not discussed.

8. Comparator

The ADAR defines the comparator as ‘usual care in the last line of therapy.’ Last line of therapy has been defined as ‘patients have trialled or are not suitable for all other treatment options.’ Usual care consists of sleep hygiene, weight and alcohol management or other lifestyle interventions.

The main comparator in MSAC Application 1595 was conservative medical management, which MSAC indicated was appropriate.

PASC “considered that ‘last line of therapy,’ ‘usual care’ and ‘no active treatment’ need to be clearly defined and consistently applied, along with explicit clarification of the differences between no active treatment versus conservative medical management.” The commentary considers that the resubmission fails to do this. The applicant’s pre-ESC response clarified that the term ‘active treatment’ was detailed in the ADAR (in the paragraph below Figure 4) as consisting of ‘Continuous positive airway pressure (CPAP), mandibular advancement splint (MAS) and surgical options.’ The ADAR has defined “no active treatment” as lifestyle interventions such as weight management, sleep hygiene, alcohol consumption management or positional therapies.

Application 1595 has a supplementary comparator of upper airway surgery represented by uvulopalatopharyngoplasty (UPPP) which has been removed as a comparator in the resubmission. PASC considered this reasonable but “indicated this would need to be articulated and justified in the resubmission assessment report.” The commentary considers that this has not been done. While acknowledging this point, the applicant’s pre-ESC response noted that the patient population definition already rules out upper airway surgery as a comparator as the definition refers to patients ‘receiving no active treatment, have trialled or are not suitable for all other treatments’. Under this scenario patients would either have had unsuccessful surgery, or not be suitable for surgery and therefore upper airway surgery would not be a comparator to UAS.

9. Summary of public consultation input

Consultation feedback further to this resubmission was received from five organisations and seven individual health professionals including a GP, specialists and surgeons. The organisations that submitted input were:

- Sleep Health Foundation
- The Australian Society of Otolaryngology Head and Neck Surgery (ASOHNS)
- Australia and New Zealand Sleep Science Association (ANZSSA)
- Australian Hypoglossal Implant Centre (AHI-C)
- The Australasian Sleep Association (ASA)

All input received indicated support for public funding for the service which was considered to be needed and clinically relevant for the proposed population.

One of the organisations considered that the service would be an important addition to the area of treating obstructive sleep apnoea. One of the organisations also considered that since there are many alternative devices to the closed loop system approved internationally, the assessment should be broader in its scope and not just consider “closed loop” devices, but be open to the use of any “hypoglossal nerve stimulation device”.

The individual surgeons and specialists were all very supportive of the service, however they shared concern regarding leakage to the general population and use in other indications outside the target patient population. They supported all efforts to carefully select patients to limit this service to those that stand to benefit the most and have exhausted all available publicly funded options for treatment. It was noted that these patients may develop other health conditions as a consequence of their sleep apnoea not being adequately treated, so having this service publicly funded will ensure that these patients are afforded a last line option which may prevent them developing comorbidities and may also reduce the cost on the health system in future.

10. Characteristics of the evidence base

The applicant undertook a literature search to update the evidence presented in Application 1595. The search identified seven studies (11 records) for inclusion. Six of the studies were not included in Application 1595; none of these were included in the clinical evaluation except in the section ‘Extended Assessment of Harms.’ The clinical evaluation almost exclusively reported the outcomes of the STAR trial, which is the same study reported in Application 1595.

A targeted, rapid search of the literature undertaken for the commentary identified multiple studies that were not included in the literature review or listed in the excluded studies list and could provide additional relevant information. The commentary has extracted data from the following studies to supplement that from the STAR trial presented by the applicant:

- Mehra (2020) – an analysis from the Adherence and Outcome of Upper Airway Stimulation for OSA International (ADHERE) registry comparing UAS against usual care identified in the applicant’s updated literature search but not reported on
- EFFECT – identified in the applicant’s updated literature search but not reported on
- ADHERE registry for safety outcomes (Thaler, 2019 and Suurna, 2020⁴) – identified in the applicant’s updated literature search but not reported on
- German post-market study (Steffen, 2019⁵) for safety outcomes– identified in the applicant’s updated literature search but not reported on
- Lorenz and Goyal (2022⁶) for safety outcomes – not identified by the applicant

⁴ Thaler E, et al. (2019). ‘Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy’, *Laryngoscope*, 130(5):1333-1338.

Suurna MV, et al. (2021) ‘Impact of Body Mass Index and Discomfort on Upper Airway Stimulation: ADHERE Registry 2020 Update’, *Laryngoscope*, 131(11):2616-24.

⁵ Steffen A, et al. (2020). ‘Long-term follow-up of the German post-market study for upper airway stimulation for obstructive sleep apnea’, *Sleep and Breathing*, 24(3):979-84.

⁶ Lorenz F. J., & Goyal N. (2022). ‘Iatrogenic Pneumothorax During Hypoglossal Nerve Stimulator Implantation: A Large Database Analysis [Article in Press]’, *Otolaryngology - Head and Neck Surgery* (United States).

- Walia (2020⁷) for cardiovascular outcomes - not identified by the applicant.

With the exception of Lorenz and Goyal (2022), all studies in Table 7 are funded by Inspire Medical Systems or the authors received consultancy fees and/or expenses from Inspire Medical Systems.

Table 7 Key features of the included evidence for closed loop UAS

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Closed loop UAS vs usual care						
Mehra (2020) (ADHERE Substudy)	UAS = 250 No intervention = 100	MC; PS, OB	<i>High</i>	OSA and PAP intolerance meeting UAS implantation criteria ^a who requested insurance preapproval for surgery	AHI ODI ESS FOSQ-10	Not used
Closed loop UAS stimulation vs sham/no closed loop UAS						
STAR (Woodson, 2014)	46	R therapy withdrawal	<i>High</i>	UAS therapy responders 12-months post-implantation	AHI ODI ESS FOSQ-10 Systolic and diastolic blood pressure	Not used
EFFECT (Heiser, 2021)	89	R crossover therapy withdrawal	<i>High</i>	Moderate to severe OSA (AHI ≥ 15), CPAP intolerance, absence of CCC during DISE and received UAS at least 6 months prior to study	AHI ODI ESS FOSQ-10	Not used
Closed loop UAS vs PAP						
Walia (2020) (ADHERE substudy)	201 per arm	MC; PS, OB; Propensity matched	<i>High</i>	UAS: ADHERE registry (patients receiving UAS who met inclusion criteria ^a) PAP: consecutive patients with OSA who initiated their first PAP treatment at Cleveland Clinic	Blood pressure ESS	Not used

⁷ Walia H. et al. (2020). 'Upper Airway Stimulation vs Positive Airway Pressure Impact on BP and Sleepiness Symptoms in OSA', *Chest*, 157(1): 173-183.

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Closed loop UAS						
STAR (Strollo, 2014; Woodson, 2018)	126	MC; PS, OB	<i>High</i>	moderate to severe OSA (AHI >20 and <50) with difficulty accepting or adhering to CPAP treatment, BMI ≤ 32.0. No anatomic abnormalities preventing UAS or complete concentric collapse of the palate	AHI ODI ESS FOSQ-10	AHI ESS
ADHERE (Thaler, 2019 and Suurna, 2020)	823	MC; PS, OB	<i>High</i>	Patients receiving UAS who met inclusion criteria ^a	Procedural and device related AEs	Not used
G-PMS (Steffen, 2019)	60	MC; PS, OB	<i>High</i>	Patients with a previous diagnosis or likely to have a diagnosis of moderate to severe OSA (AHI between 15 and 65/h) and intolerance to PAP. BMI ≤ 35 kg/m ²	Serious AEs	Not used
Lorenz and Goyal (2022)	1813	MC; OB	<i>High</i>	Patients with OSA who underwent UAS implantation	Serious AEs	Not used

AE = adverse event; AHI = Apnoea Hypopnea Index; BMI = body mass index; ccc = complete concentric collapse of the palate; DISE = drug-induced sleep endoscopy; ESS = Epworth Sleepiness Scale; MC = multicentre; OB = Observational; ODI = oxygen desaturation index; FOSQ = Functional Outcomes of Sleep Questionnaire; OSA = obstructive sleep Apnoea; PAP = positive airway pressure; PS = Prospective; R = randomised; UAS = upper airway stimulation.

Notes: a. ADHERE inclusion criteria: intolerance or suboptimal adherence to CPAP, history of moderate to severe OSA [AHI ≥15], and for whom there was observed absence of CCC with DISE.

Source: compiled for the commentary executive summary based on information in MSAC Application 1595.1 and the in-line commentary

11. Comparative safety

No comparative safety data were presented in the ADAR or identified by the commentary. The ADAR presented the 12-month safety data from the STAR study. The safety data extracted by the commentary is presented in Table 8.

Non-serious device related adverse events affect a substantial number of patients with discomfort due to the electrical stimulation and tongue abrasion being most common. Procedure related data demonstrates a relatively low risk of complications.

As a permanently implanted medical device, there is an ongoing risk of complications with revision and explant rates likely to increase over time. The commentary considers that the long-term follow-up data on such outcomes remains poorly reported.

Table 8 Summary of safety outcomes

Study reference Follow-up (N)	Serious Adverse event (No. of events, %)	Procedure related non- serious adverse event	Device related non-serious adverse event
STAR (Strollo, 2014, Woodson, 2018) 12 months (124) 5-years (97)	Follow-up period Lead or device reposition or replacement (9 events, 8 patients, 6%) Device explant (3, 2%) Death, unrelated (5, 4%)	Post-operative discomfort or symptoms (142, 80%) Tongue weakness (34, 18%) Mild infection (1, <1%)	Discomfort due to electrical stimulation (142, 60%) Tongue abrasion (49, 27%) Dry mouth (20, 15%) Pain (14, 11%) Device usability (70, 43%) Infection (1, <1%) Other (39, 25%)
G-PMS (Steffen, 2019) 32 months (60)	Follow-up period Sensing lead replacement (2, 3%) Device explant (2, 3%) Death, unrelated (1, <1%)	NR	NR
ADHERE (Thaler, 2019, Suurna, 2020) ^a 6 months (350) 12 months (353) (Thaler, 2019) 12 months (823) (Suurna, 2020)	Intraoperative Hematoma (8, 0.43%) Infection (2, 0.11%) Pneumothorax (1, 0.05%) Other (4, 0.16%) Follow-up period System explant (1, 0.05%) System revision (3, 0.16%) Sensor lead revision (12, 0.70%) Stimulation lead revision (12, 0.64%) IPG pocket revision (2, 0.11%) Other (4, 0.16%)	Post-operative discomfort or symptoms (42, 11%) Tongue weakness (3, <1%) Infection (2, <1%) Other (5, 1%)	Discomfort due to electrical stimulation (69, 20%) Tongue abrasion (26, 7%) Device discomfort (15, 4%) Insomnia/arousal (27, 8%) Other (discomfort, activation) (80, 23%)
Lorenz and Goyal (2022) NR – range 8 years to 1 month (1,813)	Intraoperative (to 3 months) Pneumothorax 44 (2.4%) Pleural effusion 11 (0.6%) Infection 17 (0.9%) Follow-up period Revisions or replacements 25 (1.4%) Explants 22 (1.2%)	NR	NR

Note: a. The denominator for the ADHERE safety data is unclear; percentages are reported as per the study. In Thaler (reporting non-serious AEs), there were 640 patients who completed 6-month follow-up and 382 for 12-month follow-up, however, safety data was reported only for those patients who completed the visit form. This number is not reported in the study and has been estimated from the rates presented in the paper. In Suurna (reporting serious AEs), total number of patients enrolled was (1,849) and 823 completed the 12-month follow-up (the number who completed the visit form is NR). Source: Commentary Table 5 of MSAC Application 1595.1

12. Comparative effectiveness

Apnoea hypopnea index (AHI)

Mean change in AHI is a key input into the economic model and therefore a critical effectiveness outcome. The ADAR has not defined a clinically important change in AHI, although the threshold for moderate OSA is ≥ 15 . Although AHI is diagnostic for OSA, it is a surrogate measure for health outcomes.

The ADAR reported the mean change at 5 years from the STAR study of -17.1 ± 1.7 (95% confidence interval (CI) -20.5 to -13.6). It also reported on the STAR therapy withdrawal trial (Table 10).

The commentary provided additional evidence from the Mehra (2020) non-randomised comparative study (Table 9) and the EFFECT trial (Table 10). All show a statistically significant difference in mean change in AHI from baseline for UAS compared with either usual care or sham/no treatment.

Table 9 Change in AHI for the non-randomised comparative study (UAS vs usual care)

Study ID	Risk of Bias	Study arm	Baseline (mean \pm SD)	Final Visit (mean \pm SD)	Change (mean \pm SD)	Absolute difference (mean \pm SD)	P Value
Mehra (2020)	High	Intervention (UAS, n=228)	33.7 \pm 13.4	14.7 \pm 13.8	-19.1 \pm 15.8		
		Comparator (Usual care, n=100)	34.9 \pm 16.4	26.8 \pm 17.6	-8.1 \pm 20.9	11.0 \pm NR	P < 0.001

Abbreviations: AHI, Apnoea hypopnoea index; NR, not reported; SD, standard deviation; UAS, upper airway stimulation.
Source: Commentary Table 6 of MSAC Application 1595.1

Table 10 Change in AHI for the randomised controlled therapy withdrawal trials

Study ID	Risk of Bias	Study arm	Baseline (mean \pm SD)	Follow-up/ 1 week (mean \pm SD)	Change (mean (95% CI or \pm SD))	Absolute difference (mean (95% CI))	P Value (on vs off at follow-up)
STAR (Woodson, 2014)	High	'on' therapy (n=23)	7.2 \pm 5.0	8.9 \pm 9.1	1.7 \pm 6.4		
		'off' therapy (n=23)	7.6 \pm 4.0	25.8 \pm 16.2	18.2 \pm 15.6	-16.5 \pm NR	<0.001
EFFECT (Heiser, 2021)	High	Stim (n=86)	8.3 \pm 8.9	8.9 \pm NR	0.6 (-1.8, 2.9)		
		Sham (n=86)	8.3 \pm 8.9 ^a	24.4 \pm NR	16.1 (13.7, 18.4)	-15.5 (-18.3, -12.8)	<0.001

Abbreviations: AHI, Apnoea hypopnoea index; CI, confidence interval; NR, not reported; SD, standard deviation; UAS, upper airway stimulation.

Notes: a. Baseline AHI is the same for stim and sham arms of the EFFECT trial due to the cross over design. All patients received stim for 1 week and sham for 1 week with the order randomised. The analysis presented is for the total participants (n=89), each contributing to both the sham and the stim arm.

Source: Commentary Table 7 of MSAC Application 1595.1

The primary outcome of the EFFECT trial was the number of responders (defined as AHI ≤ 15) which was 73.3% (33/45) in the UAS stimulation group and 29.5% (13/44) in the UAS sham stimulation group, a difference of 43.8% (95% CI 25.1–62.5, p < 0.001) between the parallel randomised groups based on intention-to-treat analysis.

The additional evidence is of a similar magnitude and direction to the STAR study.

The comparative non-randomised study (Mehra, 2020) is at high risk of bias due to differences in the selection of patients in the two arms but is the most applicable study with respect to the specified population and comparator and therefore should have been considered in the

economic analysis. The applicant’s pre-ESC response indicated that they believed that the current analysis is justified and more appropriate than using an analysis based on Mehra et al. study data. The applicants noted that use of the Mehra et al. 2020 data would have led to a more favourable result for effectiveness as the mean change in AHI was greater than in the STAR trial data used. Furthermore – different from the STAR trial - no long-term follow-up is available from the Mehra et al. study.

The two randomised therapy withdrawal trials are less relevant to the PICO, are in highly selected patients who have already been implanted with a device and, in the case of the STAR study, are known responders. Both trials have insufficient follow-up for a long-term device.

Mean change in ODI was reported for the same studies and also shows a statistically significant effect for UAS.

Health Related Quality of Life

Health related quality of life was measured using the Epworth Sleepiness Scale (ESS), which measures self-reported sleepiness, and by the Functional Outcomes of Sleep Questionnaire (FOSQ), which measures disease specific quality of life.

The ADAR reported ESS for the STAR trial only. The commentary has provided additional data in Table 11 and Table 12, all of which demonstrate a statistically significant effect for UAS. A statistically significant effect was also found across all studies for FOSQ. In none of the studies was it possible to blind patients to the intervention they were receiving, and therefore these subjective outcomes are at a higher risk of bias than the other outcomes.

Table 11 Change in ESS for the non-randomised comparative study (UAS vs usual care)

Study ID	Risk of Bias	Study arm	Baseline (mean ± SD)	Final Visit (mean ± SD)	Change (mean ± SD)	Absolute difference (mean ± SD)	P Value
Mehra (2020)	High	Intervention (UAS, n=226)	12.3 ± 5.5	7.2 ± 4.8	-5.1 ± 5.5		
		Comparator (Usual care, n=90)	10.9 ± 5.4	12.8 ± 5.2	1.8 ± 3.7	6.9 ± NR	P < 0.001

Abbreviations: ESS, Epworth Sleepiness Scale, NR, not reported; SD, standard deviation; UAS, upper airway stimulation. Source: Commentary Table 10 of MSAC Application 1595.1

Table 12 Change in ESS for the randomised controlled therapy withdrawal trials

Study ID	Risk of Bias	Study arm	Baseline (mean ± SD)	Follow-up/ 1 week (mean ± SD)	Change (mean (95% CI))	Absolute difference (mean (95% CI))	P Value (on vs off at follow-up)
STAR (Woodson, 2014)	High	'on' therapy (n=23)	5.9 ± 3.4	5.6 ± 3.9	-0.3 ± 1.8		
		'off' therapy (n=23)	6.9 ± 4.6	10.0 ± 6.0	-3.8 ± 4.6	3.5 ± NR	.005
EFFECT (Heiser, 2021)	High	Stim (n=86)	7.0 ± 4.4	NR	-0.2 (-0.7, 1.1)		
		Sham (n=86)	7.0 ± 4.4	NR	-3.5 (2.6, 4.4)	3.3 (4.4, 2.2)	<0.001

Abbreviations: CI, confidence interval; ESS, Epworth Sleepiness Scale, NR, not reported; SD, standard deviation; UAS, upper airway stimulation.

Source: Commentary Table 12 of MSAC Application 1595.1

Cardiovascular outcomes

Cardiovascular outcomes were requested in the PICO Confirmation but were not reported in the ADAR. These outcomes are important because they are health outcomes whereas AHI and ODI are surrogate measures.

The STAR trial reported change in blood pressure and found no significant difference in the randomised controlled therapy withdrawal trial and at 12-months in the single arm study.

The commentary identified a study that reports on changes in blood pressure following UAS (Walia, 2020). The study is a propensity matched cohort comparing UAS and positive airway pressure (PAP) using data from the ADHERE registry for the UAS arm. The mean follow-up for the PAP group was 108 days (SD, 36), and the UAS group follow-up was 134 days (SD, 76).

There was a statistically significant improvement in diastolic BP and mean arterial pressure in the PAP group but not the UAS group. Change in systolic BP was not significant for either group. Comparing the two groups, there was a statistically significant greater improvement in diastolic BP and mean arterial pressure in favour of the PAP group.

PASC included cardiovascular outcomes in the PICO as the applicant intended to include evidence from the CARDIOSA-12 trial, which aims to assess the impact UAS on blood pressure and other cardiovascular endpoints. This was a double-blinded, sham-controlled, randomised therapy crossover trial with 53 subjects randomised to four weeks in each arm; “active” or “sham.” The ADAR does not mention this trial, but the commentary has identified an abstract of the findings. Results were also published on clinicaltrials.gov on 6th December 2022.

The abstract⁸ reports that:

- There was no significant difference in mean 24-hour systolic BP between “active” and “sham” UAS (122.4 mmHg [12.2] vs 122.4 mmHg [11.2], respectively)

⁸ Akshay Tangutur, Everett Seay, Maurits Boon, Colin Huntley, Erica Thaler, Raj Dedhia, 0785 Cardiovascular Outcomes For Obstructive Sleep Apnea With HGNS Therapy, Sleep, Volume 45, Issue Supplement_1, June 2022, Page A341, <https://doi.org/10.1093/sleep/zsac079.781>

- There was no significant difference in mean systolic BP during sleep between “active” and “sham” UAS (115.0 mmHg [15.2] vs 115.2 mmHg [14.4], respectively)

No other results were reported in the abstract. Without a full study report, the risk of bias cannot be assessed; however, the length of the intervention was longer than the one-week withdrawal in the STAR and the EFFECT study and it was not industry sponsored.

Clinical claim

Based on very low quality evidence, a claim of superior effectiveness for UAS compared with no active treatment for patients with moderate to severe OSA who have failed or are unable to tolerate CPAP may be supported in terms of surrogate outcomes (AHI and ODI) and subjective quality of life measures. However, the clinical claim is not supported for cardiovascular outcomes based on blood pressure measures and there is no evidence of superior effectiveness for long-term health outcomes.

The evidence supports a claim that UAS has inferior safety compared with no active treatment for patients with moderate to severe OSA who have failed or are unable to tolerate CPAP. This is consistent with MSAC advice for Application 1595 that the assumption is reasonable despite a lack of comparative evidence. Nevertheless, the evidence is of very low quality with insufficient follow-up for a long-term implantable device.

13. Economic evaluation

A cost-utility analysis is presented. A summary of the economic analysis is provided in Table 13.

The economic evaluation has been updated from the previous submission in line with MSACs comments that the model in Application 1595 was overly simplistic. The resubmission is based on a published model (Pietzsch; 2019⁹) which used changes in AHI to model cardiac outcomes. The resubmission has a lifetime time horizon, which does not align with MSACs request for the resubmission to use a shorter time horizon (15 or 20 years).

A Markov model is utilised to simulate disease progression. Events and outcomes are modelled for two patient cohorts with moderate to severe OSA: UAS-treated and a no active treatment comparator. The model projects three clinical events – myocardial infarction, stroke and hypertension – and the incidence of motor vehicle collisions. The choice of the events was based on the relationships that have been documented between OSA severity and event incidence. The general structure had been previously published (Pietzsch, 2009¹⁰; Pietzsch, 2015¹¹; Pietzsch, 2019). The commentary notes that these are applicant-funded cost-utility studies based on United States, German and UK costs.

⁹ Pietzsch JB, et al. Clinical and economic benefits of upper airway stimulation for obstructive sleep apnea in a European setting. *Respiration*. 2019;98(1):38-47

¹⁰ Pietzsch JB, et al. An integrated health-economic analysis of diagnostic and therapeutic strategies in the treatment of moderate-to-severe obstructive sleep apnea. *SLEEP* 2011;34(6):695-709

¹¹ Pietzsch JB, et al. 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):735-44

Table 13 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Patients ≥ 18 years of age, with a BMI ≤ 32 kg/m ² , confirmed moderate to severe OSA (equivalent to having an AHI score ≥ 15 and ≤ 65), and confirmed to either have unsuccessful or intolerable CPAP therapy or BIPAP therapy. Patients with a complete concentric collapse of the soft palate, detected through a DISE, are not eligible for UAS treatment. Patients are receiving no active treatment, have trialled or are not suitable for all other treatment options.
Prior testing	DISE, PSG and multidisciplinary meeting
Comparator	A patient cohort that does not receive the UAS intervention, but instead receives usual care in the last line of therapy, i.e., no active treatment.
Type(s) of analysis	Cost-utility analysis.
Outcomes	QALYs and costs.
Time horizon	A lifetime time horizon is utilised. The PSD for ADAR 1595 suggested a shorter time horizon of 15 years was appropriate for this intervention.
Computational method	Markov model
Generation of the base case	The base case assumes trial-observed effectiveness is maintained in patients remaining on UAS therapy. The base case transforms change in AHI into health outcomes. The base case transforms change in ESS and FOSQ into utilities.
Health states	Well, Hypertensive, Post-MI, Post-stroke and Death
Cycle length	One month
Transition probabilities	Transition probabilities were computed utilising univariate and multivariate risk equations, sourced from cohort studies and published data. Incidence of hypertension, MI, and stroke was based on Australia-specific data in the general population, and subsequently adjusted for OSA using hazard ratios from published literature for moderate to severe OSA. The incidence of MVC was derived from New South Wales Department of Transportation data and adjusted for OSA using a hazard ratio from published literature. Subjects receiving no active treatment (including those that discontinued UAS therapy) were assumed to maintain the OSA-related elevated event risks for the remainder of their lifetime. The commentary notes that this assumption implies the absence of alternative treatment approaches emerging over a lifetime horizon. It also implies a continued tolerance of UAS and persistence of treatment effect beyond the available data. For patients on UAS therapy, a reduction of the OSA-related excess event risk was calculated for MI and stroke based on a regression analysis associating AHI and cardiovascular outcomes. The commentary notes that this approach assesses the mean AHI, with non-responders not addressed separately. Elevated MVC risk was assumed to be reversed on UAS therapy, based on study reported ESS improvement that documented elimination of daytime sleepiness. The commentary considers more conservative data showing a risk reduction, but not elimination, is more current and is more appropriate to apply. Mortality was based on Australian lifetables, adjusted through condition/event-specific hazard ratios. Post-event survival was obtained from published literature. The assumptions underlying the base case scenario were further explored through sensitivity analyses.
Discount rate	5% for both costs and outcomes
Software	The analysis was conducted in TreeAge Pro, with MS Excel utilised to support data aggregation and the organisation of model inputs. Statistical analyses were performed in JMP Pro (SAS Institute).

AHI=Apnoea Hypopnea Index; AR DRG = Australian Refined Diagnosis-Related Group; BIPAP= bi-level positive airway pressure; CPAP= Continuous Positive airway pressure; DISE= drug-induced sleep endoscopy; ESS= Epworth Sleepiness Scale; FOSQ= Functional Outcomes of Sleep Questionnaire; ICER= Incremental cost-effectiveness ratio; MBS = Medicare Benefits Schedule; MI=myocardial infarction; MVC = motor vehicle collisions; OSA=Obstructive Sleep Apnoea; ODI= Oxygen Desaturation Index; PSD = public summary document; PSG = polysomnography; QALY=Quality-adjusted life year; UAS=Upper Airway Simulation.

Source: Table 22 of MSAC Application 1595.1 adapted for the Commentary executive summary

The ADAR did not present a stepped economic analysis.

The commentary notes that the cost of the device (\$30,480) is lower than that used in Application 1595 (\$36,600) as requested by MSAC for a resubmission. However, a vagal neurostimulator (PL Billing Code item SA174) is listed at \$11,435 (PL, Part A, November 2022). The MBS schedule fees were based on those for vagal stimulation, so it is worth considering if the price point chosen for the UAS device is appropriate.

The ADAR did not use the 100% MBS fees as requested by MSAC Guidelines.

The base case presented in the ADAR (lifetime time horizon) is presented in Table 14. The ADAR presented an additional analysis with a 10-year time horizon with the base case; however, the commentary prefers a 15-year time horizon as the base case as it accounts for an initial battery replacement (every 11 years) and is consistent with MSACs requests for the resubmission.

Table14 Health Outcomes and Incremental Cost-Effectiveness Results

Lifetime	Cost (\$) Discounted	Incremental Cost (AUD)	Effectiveness (QALY), Discounted	Incremental QALY	ICER (\$/QALY), Discounted
No Active Treatment	\$31,042		8.59		
UAS Treatment	\$86,749	\$55,707	9.76	1.17	\$47,662
15-Years					
No Active Treatment	\$16,142		6.41		
UAS Treatment	\$65,196	\$49,053	7.18	0.77	\$63,899

UAS; Upper Airway Stimulation; QALY=Quality-Adjusted Life Year

Note: Data shown are derived from the commentary. The values have been recalculated based on sex-weighting, as the value shown in the ADAR was for males only.

Source: Table 35 of MSAC Application 1595.1 adapted for the Commentary executive summary

Key drivers of the model are the time horizon, reduction in cardiovascular risk and utility gain. These each have a high impact on the ICER and favour UAS (Table 15).

Table 15 Key drivers of the model

Description	Method/Value	Impact Base case: \$47,662/QALY gained Commentary preferred base case: \$63,899
Extrapolation	Treatment effect continued beyond 5-year trial period to lifetime horizon or 15 years. Similarly, no treatment arm assumed to have no effect over lifetime/15 years	<i>High, favours UAS</i> <i>A time horizon of 5 years increases the ICER to \$113,845</i>
Transformation	Reduction in AHI is assumed to lead to a reduction in cardiovascular risk for UAS. No change in blood pressure has been demonstrated in trials of UAS	<i>High, favours UAS</i> <i>No reduction in CV risk from UAS increases the ICER to \$76,340</i>
Utilities	UAS-treated patients were assumed to achieve the same HRQoL as patients treated with CPAP. This assumption was made based on the STAR trial-observed improvements in values for ESS and the FOSQ	<i>High, favours UAS</i> <i>Use of a 50% gain in HRQoL increases the ICER to \$73,565/QALY gained.</i>

CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; FOSQ = ICER = incremental cost-effectiveness ratio; HRQoL = health related quality of life; QALY = quality-adjusted life year; UAS = upper airway stimulation.

Note: The values have been recalculated based on sex-weighting, as the value shown in the ADAR was for males only.

Source: developed for the Commentary Executive Summary based on information in Table 36 of MSAC Application 1595.1

The results of key univariate sensitivity analyses are summarised in Table 16.

Key concerns with the economic evaluation are the time horizon which is presented over a lifetime horizon by the applicant but the commentary considers 15-years an appropriate base case based on MSAC feedback from Application 1595, the length of follow-up available in the existing trials and the estimated time to battery replacement of 11 years. The applicant’s pre-ESC response argued that using a 15-year time horizon introduces some bias because if this shorter horizon is selected because of concern about lack of long-term therapy effect, it does not seem warranted to have the full cohort undergo a device replacement at year 11, and to then only consider 4 years of device benefit after that replacement. The pre-ESC response considered that if the 15-year scenario is preferred, the modelling scenario should not then assume that device replacement applies to the full cohort.

Secondly, the model considers that the effectiveness of UAS is maintained over time and that the reduction observed in AHI in trial data directly drives a reduction in cardiovascular events. This is inconsistent with the published literature which has not found any impact of UAS on cardiovascular outcomes. The indirectness of health effects, and the reliance on literature-based data not sourced from patients treated with UAS to source transition probabilities, leads to substantial uncertainty. However the applicant’s pre-ESC response considered that given that it is well established that patients with increasing OSA severity incur a higher burden of cardiovascular events and all-cause mortality compared to those not suffering from OSA, it is very plausible that a reversal of OSA, as measured through reduction in the number of apnea-hypopnea events per hour would contribute to a gradual reduction of the excess event risk. In further support of this proposition the pre-ESC response cited studies by Yaggi et al (2005)¹² and Buchner et al (2007)¹³. The pre-ESC response noted that the survival benefit assumed in the

¹² Yaggi HK, et al. (2005). ‘Obstructive sleep apnea as a risk factor for stroke and death’, *N Engl J Med*, 353(19):2034-41.

¹³ Buchner NJ, et al. (2007). ‘Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk’, *Am J Respir Crit Care Med*, 176(12):1274-80.

model from treating OSA was less than reported in these two studies and is therefore conservative by assumption. The pre-ESC response also noted that the 10-year event risks for stroke arising from OSA in the model are lower than reported in Yaggi et al (2005) and Young et al (2008)¹⁴ as further evidence that the ADAR model is conservative in its assumptions.

The model also does not account for non-responders (19 patients (15%) in the STAR study), nor allow for any health gains within the comparator arm. However the applicant's pre-ESC response noted that the mean effect for the full cohort already takes into consideration the effect observed in the 15% non-responders.

Finally, the safety outcomes for UAS have been poorly reported and not studied over longer time periods. The model relies on sponsor provided rates of device replacement and battery life and actual rates may differ significantly. Furthermore, lead and pulse generator repositioning or revision are not included in the model, are not infrequently reported in the literature and would add to the cost of UAS. However the applicant's pre-ESC response considered that the impact of the additional cost of lead/device repositioning costs would be small in light of very low event rates in contemporary practice, citing an event rate of around 1.5% revisions in the period through 24 months based on safety data from the applicant. The pre-ESC response also noted that based on the applicant's safety data, these event rates have been decreasing over time and that therefore evidence from published literature from some years ago will not properly reflect contemporary real-world data.

¹⁴ Young T, et al. (2008). ' Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort', *Sleep*, 31(8):1071-8.

Table 16 Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$55,707	1.17	\$47,662
Commentary base case (15 years)	\$49,053	0.77	\$63,899
Time horizon (base case lifetime)			
5 years	\$36,096	0.32	\$113,845
CV risk reduction (base case 68%)			
50% (lifetime horizon)	\$53,327	1.01	\$52,576
50% (15-year time horizon)	\$48,326	0.73	\$66,258
No CV risk reduction benefit (lifetime horizon)	\$57,915	0.76	\$76,340
No CV risk reduction benefit (15-year time horizon)	\$50,856	0.63	\$81,210
MVC risk reduction (base case 100%)			
50% (lifetime horizon)	\$57,637	1.15	\$50,216
50% (15-year time horizon)	\$50,836	0.76	\$66,607
No MVC risk reduction benefit (lifetime horizon)	\$60,027	1.16	\$51,928
No MVC risk reduction benefit (15-year time horizon)	\$52,634	0.76	\$69,150
Device price (base case \$30,480)			
Alignment with vagal neurostimulation (\$14,504, 15-year time horizon)	\$27,534	0.77	\$35,867

CV = cardiovascular; ICER = incremental cost-effectiveness ratio; MVS = motor vehicle collisions; QALY = quality-adjusted life year. Notes: The values have been recalculated from those presented in the ADAR based on sex-weighting, as the values shown in the ADAR was for males only.

Source: Table 37 and Commentary Table 17 of MSAC Application 1595.1 adapted for the commentary executive summary.

14. Financial/budgetary impacts

Although an epidemiological approach has been undertaken to estimate the eligible population, the financial implications use a market-based approach as device access is restricted due to limited access to centres providing the service and trained surgeons within those centres. The estimated utilisation due to these limitations is a very small proportion of the potentially eligible population, noting that the potentially eligible population is difficult to estimate confidently and highly uncertain.

The financial implications to the MBS and PL resulting from the proposed listing of closed loop UAS are summarised in Table 17. The impact of listing UAS on the MBS on other technologies has not been included in the analysis. In Application 1595, a reduction in UPPP surgery as a result of the introduction of UAS was modelled but this has not been included in the resubmission. It is likely that the availability of UAS would impact on rates of surgery for OSA but in which direction and to what extent is uncertain. It is possible that upper airway surgery could be used to treat complete concentric collapse of the palate and therefore enable patient eligibility for UAS; this has not been considered in the ADAR.

The financial implications are presented over 6 years (Table 17). The ADAR did not disaggregate the projected costs to show the impact of funding UAS to the MBS, PL and other health budgets and included modelled savings from reduced downstream health impacts. These are very

uncertain based on the clinical evidence and therefore have not been included in the analysis undertaken by the commentary. The commentary has added the cost of multidisciplinary case conferences, anaesthesia for DISE and screening patients with DISE who are then found ineligible for UAS.

The estimated cost to the MBS of implantation of the device is \$1,044,966 (\$52,248 in year 1 rising to \$348,322 in year 6). The estimated cost of post-implant care over six years (which includes programming, repositioning, replacement, and battery replacement) is \$174,498; however, these costs are far less certain. The estimates of repositioning and replacement in Table 17 are based on the rates of these services for vagal nerve stimulation since they were funded in 2017. All devices would need battery replacement if implanted beyond the battery lifetime, so this item would be expected to have a greater budget impact >10 years after UAS is initially funded.

The commentary estimated cost to the MBS of screening patients for eligibility for UAS is \$115,024 (\$5,751 in year 1 rising to \$38,341 in year 6). This is assuming that 75% of those screened with DISE are implanted (based on Strollo, 2014), however, this rate is uncertain.

The commentary estimates the total cost to the MBS over six years as \$1,334,488 based on the rates of uptake provided in the ADAR.

The cost to the PL is much greater than to the MBS. At the proposed cost of \$30,480, the cost to the PL is \$18.288 million over six years (\$914,400 in year 1 rising to \$6,096,000 in year 6).

The applicant's pre-ESC response noted that the applicant would be happy to support limitations on utilisation so the Australian government is able to accurately predict and control budget impact.

Table 17 Net financial implications of UAS to the MBS and Prostheses List

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people eligible for UAS	45827	46239	46656	47075	47499	47927
Number of treatment centres	3	5	7	10	15	20
Number of people who receive UAS	30	50	70	100	150	200
Number of services of UAS per patient	1	1	1	1	1	1
Cost to the MBS – Device implant						
DISE (MBS 41764 75% fee \$97.40)	\$2,922	\$4,870	\$6,818	\$9,740	\$14,610	\$19,480
Bronchoscopy (MBS 38419 75% fee \$141.15, used by 50% of patients)	\$2,117	\$3,529	\$4,940	\$7,057	\$10,586	\$14,114
Initiation of anaesthesia (MBS 20320 75% fee \$94.30)	\$2,829	\$4,715	\$6,601	\$9,430	\$14,145	\$18,860
Anaesthesia time units (MBS 23035 75% fee \$47.15)	\$1,415	\$2,358	\$3,301	\$4,715	\$7,073	\$9,430

Case conference (MBS 822 85% fee \$190.40, MBS 10957 85% fee 75.30)	\$7,971	\$13,285	\$18,599	\$26,570	\$39,855	\$53,140
UAS implantation (proposed 75% MBS fee \$869.24)	\$26,077	\$43,462	\$60,847	\$86,924	\$130,386	\$173,848
Anaesthesia for implantation (MBS 20320 + MBS 23091 75% fee \$235.75)	\$7,073	\$11,788	\$16,503	\$23,575	\$35,363	\$47,150
Chest X-ray (MBS 58500 75% fee \$27.60)	\$828	\$1,380	\$1,932	\$2,760	\$4,140	\$5,520
Neck X-ray (MBS 57945 75% fee \$33.90)	\$1,017	\$1,695	\$2,373	\$3,390	\$5,085	\$6,780
Total implant:	\$52,248	\$87,081	\$121,913	\$174,1613	\$261,242	\$348,322
Cost to the MBS – post-implant						
Programming device (MBS 105, twice in first year then annual, 85% fee \$39.25)	\$2,355	\$5,103	\$8,635	\$13,738	\$21,588	\$31,400
UAS lead repositioning (75% fee \$480, 11% of implants)	-	-	-	-	-	\$31,680
UAS device repositioning or removal (75% fee \$126.50, 32% of implants)	-	-	-	-	-	\$24,288
UAS battery replacement (75% fee \$270.55, 22% of implants)	-	-	-	-	-	\$35,713
Cost to the MBS – Eligibility screening (but not implanted)						
Number screened (25% of those screened with DISE are not implanted - STAR study (Strollo, 2014))	10	17	23	33	50	67
DISE (MBS 41764 75% fee \$97.40)	\$974	\$1,623	\$2,273	\$3,247	\$4,870	\$6,493
Bronchoscopy (MBS 38419 75% fee \$141.15, used by 50% of patients)	\$706	\$1,176.17	\$1,647	\$2,352	\$3,529	\$4,705
Initiation of anaesthesia (MBS 20320 75% fee \$94.30)	\$943	\$1,572	\$2,200	\$3,143	\$4,715	\$6,287
Anaesthesia time units (MBS 23035 75% fee \$47.15)	\$472	\$786	\$1,100	\$1,572	\$2,357	\$3,143
Case conference (MBS 822 85% fee \$190.40, MBS 10957 85% fee 75.30)	\$2,657	\$4,428	\$6,199	\$8,857	\$13,285	\$17,713
Total screening:	\$5,751	\$9,585	\$13,419	\$19,171	\$28,756	\$38,341
Cost to the Prostheses List						
Device listed at \$30,480 (proposed)	\$914,400	\$1,524,000	\$2,133,600	\$3,048,000	\$4,572,000	\$6,096,000
Device listed at \$14,504 (vagal neurostimulator benefit)	\$435,120	\$725,200	\$1,015,280	\$1,450,400	\$2,175,600	\$2,900,800

MBS = Medicare Benefits Schedule; UAS = upper airway stimulation.

Source: prepared for the commentary from the provided excel workbook titled 'Input Book OSA Model adaption' tab 'UAS Australia cost.'

The ADAR did not discuss or estimate patient out of pocket costs although PASC noted that out of pocket costs may be substantial for UAS.

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Item Descriptor issues

- The ADAR proposes new item descriptors for case conferencing which are not needed as the MBS has existing items that would cover the case conference. However the item descriptors for UAS should specify the requirement for a case conference as requested by PASC. Identification of the required expertise in the multidisciplinary team should be detailed in an MBS explanatory note (although noting that this information was specified in the applicant's pre-ESC response).
- The ADAR does not update the item descriptor as requested by PASC to specify that patients "must have attempted all other appropriate interventions and be currently untreated" or to present the definition of Continuous Positive Airway Pressure (CPAP) failure or intolerance as agreed by PASC.
- The once per lifetime restriction is inappropriate for the item descriptor for repositioning and battery changes given that the minimum estimated longevity from the STAR trial is 7 years.
- Surgical assistance for surgical services and anaesthesia for device replacement are likely to be needed for the new service and should be costed.
- No item descriptors have been proposed for repositioning or removal of the leads (repositioning and removal of leads should also be costed).

Clinical issues:

- The resubmission does not address the uncertainty regarding the use of DISE, as requested by MSAC in the previous submission.
- The ADAR does not define a subpopulation of patients who have failed all other medical management options where UAS therapy may be appropriate.
- The literature review and clinical trial data remain inadequate and incomplete, including high risk of bias and lack of long-term follow-up data.

Economic issues:

- The ICER estimated by the economic model is driven by a reduction in AHI leading to a lower risk of cardiovascular events and a reduction in ESS leading to a reduction in the risk of motor vehicle accidents. The evidentiary basis behind both these assumptions is uncertain.
- The economic model in the resubmission does not reduce the time horizon to 15 years as requested by MSAC.

Financial issues:

- The costs to the MBS and the Prostheses List are substantial and may be underestimated.
- Out of pocket costs for the device may be substantial if it is not recommended for listing on the Prostheses List.
- There is a risk of leakage to a broader population.

ESC discussion

ESC noted that this was a resubmission to request Medicare Benefits Schedule (MBS) listing of closed loop upper airway stimulation (UAS) for moderate to severe obstructive sleep apnoea (OSA), in patients who have failed or are intolerant to, continuous positive airway pressure (CPAP) therapy. The previous submission had been considered by [MSAC in November 2020](#), and MSAC had not recommended MBS funding. MSAC's requirements for a resubmission are shown in ESC Table 1.

ESC Table 1 Requirements for a resubmission for application 1595

Item	MSAC advice
Use of DISE as a prior test	Address the uncertainty regarding the use of DISE as raised by ESC
Population and clinical place	There may be a subpopulation of patients who have failed all other medical management options where UAS therapy may be appropriate. The resubmission would need to define this subpopulation using the appropriate eligibility criteria.
Clinical evidence	Provide evidence to support use of UAS in this refined population
Economic evaluation	Improve the economic model to address the uncertainties regarding the model structure, time horizon (and device replacement due to end battery life), effect size (AHI/mortality) estimate as raised by ESC. The resubmission should also reduce the cost of the device in order to ensure cost-effectiveness
Financial estimates	Update, as required (see above)

Abbreviations: AHI=apnoea hypopnoea index; DISE=drug induced sleep endoscopy; UAS=upper airway stimulation

Source: [Public Summary Document for application 1595, page 4](#)

ESC noted the consultation feedback received from organisations and individual clinicians. All submissions indicated support for public funding for patients who have few options left. However, several submissions expressed concern about leakage to a broader population.

ESC noted that the applicant had included two proposed MBS item descriptors for a case conference for a duration of 10 minutes or more to be attended by at minimum an ENT surgeon and a sleep physician; however, the MBS has existing items that would cover the case conference, so these additional items were not required although the item descriptors for UAS should specify the requirement for a case conference as requested by PASC. ESC also noted that other information requested by PASC was not included, including identification of the required expertise in the multidisciplinary team in an MBS explanatory note (although this was specified in the applicant's pre-ESC response), and whether a reference to "assistance on operation" should be added.

ESC noted that the ADAR did not update the item descriptor for the implantation procedure as requested by PASC to specify that patients "must have attempted all other appropriate interventions and be currently untreated" or to present the definition of Continuous Positive Airway Pressure (CPAP) failure or intolerance as agreed by PASC.

The applicant had also included new items for surgical repositioning or removal of the pulse generator, and battery replacement, as requested by MSAC. ESC queried whether "once per

lifetime” was appropriate to include in the surgical repositioning or removal of the UAS device item or for the replacement of the UAS device, as this may be required more than once during a lifetime, given that the minimum estimated longevity of the device from the STAR trial is 7 years. The applicant’s pre-ESC response stated that contemporary revision rates are around 1.5% in the 24 months following implantation. ESC confirmed that the procedure would be a same-day outpatient procedure, and that co-claiming restrictions should be in place for the proposed item for surgical placement of the UAS device and the proposed item for the repositioning or removal of the UAS device.

ESC noted that the item descriptors for the three proposed surgical services do not include a surgical assistance component, and the item descriptor for the replacement of the device does not allow anaesthesia to be claimed with this service. The Department noted that the existing item descriptors for vagus nerve stimulation (MBS items 40701, 40702 and 40704, which the proposed items are based on) include the ability to claim the assistance and anaesthesia component. ESC requested that the applicant confirm whether surgical assistance and anaesthesia are required as part of the proposed surgical services and whether this has been included in the costs. ESC also noted that the proposed MBS fee for initial insertion does not align with the existing items for vagus nerve stimulation.

ESC noted as per the Commentary that no item was proposed for repositioning or removal of the leads. ESC also noted as per the commentary that while no item has been proposed which aligns with item 40707 for electrical analysis and programming of the device, the Ratified PICO Confirmation specified that MBS item 105 could be claimed for programming of the device or for electrical analysis and programming of the device.

ESC noted the proposed clinical management algorithm. Drug-induced sleep endoscopy (DISE) remained as a prior test in the resubmission, and ESC did not consider that the applicant had adequately addressed MSAC’s concerns about the use of DISE as a prior test. In particular, ESC noted that the ADAR did not provide any additional information on the current and proposed role of DISE although it is included in the clinical algorithm. ESC also did not consider that the ADAR had addressed MSAC’s request to define a specific subpopulation who have failed all other medical management options where UAS therapy may be appropriate. ESC also considered that the comparator was not clearly defined, although this has little impact on the clinical or economic evaluations.

Overall, ESC considered that the evidence base was incomplete. ESC noted the various issues raised by the commentary about the literature review and clinical trial data. The literature review in the ADAR was conducted as a supplement to the review completed in 2019 (which the commentary to application 1595 had considered inadequate). None of the 12 new studies identified in the updated literature review had been integrated into the evidence synthesis for this resubmission. The commentary noted that most of the new studies identified by the applicant did not match the PICO criteria, and that multiple other studies were available that were not included in the literature review, were not listed in the excluded studies list, and which could provide additional relevant information. None of these studies had undergone a risk of bias assessment, but all were small, imprecise, manufacturer-sponsored and lacked sufficient follow-up data. In addition, the resubmission continued to rely on the STAR trial¹⁵ as the primary source of clinical data. ESC noted that the STAR trial was considered to have a high risk of bias and had

¹⁵ Single arm: Strollo Jr PJ, et al. (2014). ‘Upper-airway stimulation for obstructive sleep Apnoea’, *New England Journal of Medicine*, 370(2):139-49. Randomised sub-study: Woodson B et al. (2014). ‘Randomized controlled withdrawal study of upper airway stimulation on OSA: short- and long-term effect’, *Otolaryngology--head and neck surgery*, 151(5):880-7.

uncertain relevance to the PICO criteria. ESC also noted that two new trials mentioned in the PICO confirmation (EFFECT¹⁶ and CARDIOSA-12) were not included in the resubmission.

ESC noted the data on comparative safety, and agreed with the commentary that this was incompletely reported, and that long-term follow-up data remain poorly reported in the literature in the sense that there has been a lack of such data. ESC noted that the procedure-related safety data show a low risk of complications in the short-term, but the ADAR did not consider the ongoing risk of complications from UAS as a permanently implanted device. In addition, the impact of UAS as an implanted device on the ability for a patient to undergo magnetic resonance imaging (MRI) may vary by device. ESC agreed with the commentary that the clinical claim of inferior safety was supported, but that the evidence was of very low quality with insufficient follow-up for a long-term implantable device.

ESC noted the data on comparative effectiveness, and agreed with the commentary that the newly included studies showed a change in apnoea hypopnoea index (AHI) of similar magnitude and direction to the STAR trial; however, the studies had a high risk of bias and uncertain relevance to the PICO. The change in oxygen desaturation index (ODI) was consistent and showed a statistically significant effect of UAS. The changes in Epworth Sleepiness Scale (ESS) and quality of life outcomes showed a significant effect for UAS, but studies were unblinded and had a high risk of bias. The commentary also noted that cardiovascular outcomes were requested in the PICO confirmation but had not been reported in the ADAR. Studies identified by the commentary showed no significant difference in cardiovascular endpoints following UAS. ESC agreed with the commentary that the clinical claim of superior effectiveness may be supported for surrogate outcomes (AHI, ODI, quality of life), but was not supported for cardiovascular outcomes based on blood pressure endpoints, and there is no evidence of superior effectiveness for long-term health outcomes.

ESC noted as per the commentary that the section entitled 'Extended assessment of harms' in the ADAR was misnamed as most of the evidence presented was on effectiveness and it was not appropriate to present additional evidence into a separate section without integrating it into the assessment.

ESC noted that the economic evaluation in the resubmission was a cost-utility analysis. The applicant had updated the economic model from the previous submission; the resubmission was based on a sponsor-funded published model by Pietzsch et al. (2019)¹⁷. ESC noted that as per the commentary, a more complex model has been presented in the ADAR but that this does introduce further parameter uncertainty as most inputs are not taken from studies which directly relate to the specified PICO.

ESC noted that the economic evaluation used a five state Markov model. ESC noted that the model used a surrogate outcome (changes in AHI) to drive changes in cardiovascular outcomes, but noted that clinical evidence for cardiovascular outcomes was lacking, and this favoured UAS. ESC noted that in the model, motor vehicle accidents (MVA) were included as events and UAS was assumed to reduce MVA risk in the treated population to the level of the underlying population MVA risk through reductions in ESS. ESC noted the robust evidence associating sleep apnoea with motor vehicle collisions. However, ESC considered that there is no UAS-specific

¹⁶ Heiser C, et al. (2021). 'Effect of upper airway stimulation in patients with obstructive sleep Apnoea (Effect): a randomized controlled crossover trial', *Journal of clinical medicine*, 10(13): 2880.

¹⁷ Pietzsch JB, et al. et al. Clinical and economic benefits of upper airway stimulation for obstructive sleep apnea in a European setting. *Respiration*. 2019;98(1):38-47.

evidence to support the model assumptions, which are uncertain and rely on inferring direct relationships from indirect evidence.

ESC also noted that the model used a lifetime time horizon, which does not align with MSAC's request to use a shorter time horizon (15 or 20 years) and favoured UAS. ESC noted the applicant's pre-ESC response considered that a 15 year time horizon would be biased against UAS as it only allowed for an additional 4 years for use of the replaced device (assuming battery replacement every 11 years). ESC noted that the model assumed that UAS would achieve the same utility value as CPAP, but queried whether this was appropriate, given the different mechanisms of action of UAS and CPAP; this also favoured UAS. ESC also noted that the "no treatment" arm had no change over a lifetime (i.e. it was assumed that the "no treatment arm" would experience no improvements in health outcomes over their lifetimes), but ESC did not consider this to be appropriate, as weight loss or other changes may improve AHI over time. ESC noted that the model results were driven by time and device cost. In particular, ESC noted that the base case ICER estimated was \$47,662 per QALY. This rose to \$63,899 per QALY if the time horizon was reduced from a lifetime to 15 years but fell to \$35,867 per QALY (under a 15 year time horizon) if the cost of the device was aligned with vagal neurostimulation at \$14,504 instead of the applicant proposed device cost of \$30,480. ESC also noted that assuming no cardiovascular risk reduction under a 15 year time horizon increased the ICER to \$81,210 per QALY.

ESC noted the financial and budgetary impacts and in particular the commentary's estimate of a total cost to the MBS over six years of \$1,333,4688 based on uptake rates provided in the ADAR. Although an epidemiological approach was undertaken to estimate the eligible population, the financial implications used a market-based approach, as device access would be restricted due to limited access to centres providing the service and trained surgeons within those centres. ESC noted the equity issues relating to patient access, as centres would likely be limited to major metropolitan areas. The applicant estimated that each centre would treat 10 patients per year, but ESC noted that international data show an average of 20 patients treated per centre per year, so this may be an underestimate. ESC noted that there was a significant increase in post-implant costs to the MBS from year 5 to year 6 (from \$21,588 to \$123,081) due to lead revision and replacement costs. ESC noted the costs to the Prostheses List (PL) rose from \$914,400 in year 1 to more than \$6 million in year 6 if the device was listed at the proposed fee of \$30,480.

ESC noted that out-of-pocket costs for patients were likely to be substantial if the device is not included on the PL. ESC considered the high risk of leakage to a broader population, noting that sleep apnoea is a highly prevalent condition, that failing or not tolerating CPAP is common (and the definition of "not tolerating" is poorly defined), and that general surgeons (not only ear, nose and throat specialists) can implant devices subcutaneously.

17. Applicant comments on MSAC's Public Summary Document

The applicant did not offer a comment on the Public Summary Document.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)