Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1595 – Closed loop upper airways stimulation for moderate to severe obstructive sleep apnoea

Applicant: **Inspire Medical Systems Inc.**

Date of MSAC consideration: **MSAC 80th Meeting, 26-27 November 2020**

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 of closed loop upper airway stimulation (UAS) for patients who have failed or are intolerant to continuous positive airways pressure (CPAP), for the treatment of moderate to severe obstructive sleep apnoea (OSA) was received from Inspire Medical Systems Inc. by the Department of Health.

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support the creation of a new MBS item for closed loop upper airways stimulation (UAS) for moderate to severe obstructive sleep apnoea (OSA). MSAC considered the evidence did not demonstrate that the safety and effectiveness of UAS in the proposed MBS population had been established. However, MSAC noted there may be a subpopulation of patients who have failed all other medical management options where UAS therapy may be appropriate, but that this population was not clearly defined in the application. MSAC considered there were significant issues with the economic modelling, resulting in high and uncertain incremental cost-effectiveness ratios (ICERs).

Consumer summary
Inspire Medical Systems Inc. applied for public funding via the Medicare Benefits Schedule (MBS) for closed loop upper airways stimulation (UAS) for moderate to severe obstructive sleep apnoea (OSA). OSA 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 OSA, people have greater than 15 to 30 episodes of airway blockage every hour, which leads to poor sleep.

Consumer summary

Closed loop UAS aims to stimulate a person's hypoglossal nerve when they are asleep. The hypoglossal nerve controls muscles in the upper airway and base of the tongue. The UAS system is a device that has to be inserted during surgery. It has a lead that senses the person's breathing. When breathing stops, the intent of the device is to send a mild electrical signal through another lead to the hypoglossal nerve, stimulating the nerve and opening the airways, which may allow the person to breathe more easily.

The Medical Services Advisory Committee (MSAC) considered that the evidence in the application did not show that closed loop UAS is safe and effective for most people. Some patients improved after using the device, but others did not improve, and some people got worse. MSAC noted there may be a subgroup of patients that UAS would be appropriate for, but this was not shown in the application.

MSAC also noted there were critical issues with the economic model that made it very uncertain if UAS would be good value for money.

MSAC's advice to the Commonwealth Minister for Health

MSAC did not support MBS funding for closed loop UAS for people with moderate to severe OSA. This is because MSAC was not convinced that UAS was safe and effective for everyone, and was not sure if it would be good value for money.

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

MSAC noted the purpose of the application requesting MBS listing of closed loop UAS for patients who have failed or are intolerant to CPAP, for the treatment of moderate to severe OSA.

MSAC noted that drug-induced sleep endoscopy (DISE) is a required prior test for closed loop UAS, but DISE is not listed on the MBS and little is known about its utilisation.

MSAC noted that OSA has significant morbidity. MSAC noted the estimated prevalence of OSA in Australia ranges from 4.7% (2.2% for women and 7.2% for men, Deloitte 2011) to 8.3% (3.7% for women and 12.9% for men, Sleep Health Survey of Australian Adults 2016).

MSAC considered the main comparator (conservative medical management, i.e. medical management strategies [MMS]) to be appropriate, noting it may include weight and alcohol reduction, sleep positioning therapy, sleep hygiene education, and use of mandibular advancement appliances. MSAC noted the application used the embedded randomised withdrawal study in the STAR trial to demonstrate treatment effect of the closed loop UAS with medical management. The commentary considered that the literature searches were not satisfactory. However, MSAC was not aware of any additional trials that could have been included in the assessment.

MSAC noted that the STAR trial excluded patients with an apnoea–hypopnoea index (AHI) of less than 20, although the current application is for patients with AHI ≥15. MSAC also noted that patients were eligible for the trial if they "had difficulty accepting or adhering to CPAP treatment"; MSAC considered that the generalisability of this to the proposed Australian population was unclear. MSAC considered that duration of follow-up in the STAR trial was adequate, but noted that, at the 5-year time point, only 56% of study participants (n = 71) completed a polysomnography (PSG) sleep study.

MSAC noted that the ADAR did not compare closed loop UAS with uvulopalatopharyngoplasty (UPPP, supplementary comparator) as the SKUP trial had substantial differences to the STAR trial in terms of differences in baseline characteristics, use of DISE and follow-up times.

MSAC reviewed the comparative safety, noting that after 5 years follow-up from the STAR trial, 8/126 (6%) had 9 serious device related adverse events requiring surgical repositioning or replacement. MSAC also noted from a systematic review (Certal 2015), 9/200 (4.5%) patients had serious device-related adverse events that led to removal of the device. MSAC agreed with ESC and considered the claim of inferior safety of closed loop UAS compared with medical management to be reasonable.

MSAC reviewed the comparative effectiveness, noting that, overall, patients improved over 12 months using closed loop UAS, as measured by AHI, oxygen desaturation index (ODI), Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ). However, some patients did not respond, and others deteriorated. MSAC agreed with ESC that the withdrawal study did not demonstrate that closed loop UAS was superior to medical management. MSAC noted ESCs concerns that ESS is a subjective measure, but considered that this is the most commonly used measure of sleepiness.

MSAC reviewed the economic evaluation, noting translation issues relating to the generalisability of the population in the STAR trial to the proposed Australian population. MSAC agreed with ESC that:
- the economic model was overly simplistic- alternative models have relevant health states noting the National Institute for Clinical Excellence (NICE) model for CPAP in OSA (McDaid 2009) uses blood pressure to drive cardiac (Framingham equation) and stroke events; whereas Pietzch et al. 2015 uses changes in AHI. MSAC noted that ESS is the only trial outcome in the model and queried if AHI should also be included
- that the 45-year time horizon was too long, and
- that the effect size of UAS on mortality estimated from longitudinal population study (Young 2008) may be overestimated.

Furthermore, MSAC noted the economics was driven by a reduction in mortality from UAS but noted that the STAR trial did not assess mortality or cardiac event outcomes, though Woodson 2014 described blood pressure measurements. MSAC also noted the SAVE study – a large trial of CPAP in patients with cardiovascular disease – showed no effect of CPAP on mortality or cardiovascular outcomes[1]. However, MSAC considered that the SAVE patient population was considerably different to the proposed population for this application.

MSAC noted the applicant's pre-MSAC response, including additional sensitivity analyses relating to the time horizon (20 years) and mortality hazard ratios, as well as further sensitivity analyses by the Department to include ICERs over 15 years - also agreed by ESC as an appropriate time horizon. MSAC noted that the ICER was highly sensitive to these changes and up to three times the base case in some scenarios. MSAC also noted the largest cost is the device itself and advised that the device cost would need to be substantially reduced to achieve cost-effectiveness if it was to be considered by the Prostheses List Advisory Committee (PLAC) for listing on the Prostheses List.

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[1] McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS; SAVE Investigators and Coordinators. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med. 2016 Sep 8;375(10):919-31. doi: 10.1056/NEJMoa1606599. Epub 2016 Aug 28. PMID: 27571048.

MSAC noted the application did not use the prevalence data from the Deloitte report (2011), but used data from sleep studies and estimated that the eligible population would be around 20,000 people. MSAC noted the utilisation estimates indicating that the eligible patient population is very large and was concerned there would be issues with equitable access given the predicted capacity of treatment centres indicates only 0.7% of the estimated eligible patients would receive the intervention. MSAC considered that utilisation is likely to be limited by the capacity of treatment centres and specialists. MSAC considered that the costs to the MBS, and in particular private health insurance, were substantial given the low estimated number of patients who were estimated to receive the device.

MSAC considered that the place of closed loop UAS in clinical management would be as a last resort for patients who had failed all other conservative medical management options. MSAC queried whether a subgroup of patients could be identified for whom closed loop UAS is a last resort, as a way to restrict the eligible population.

MSAC considered that any resubmission would need to refine and clearly define the eligible population, including the use of DISE (which is not listed on the MBS) and potentially restrict the population to a subgroup for whom closed loop UAS is a last resort. The resubmission would also need to provide evidence to support use in this refined population and the criteria/mechanisms to ensure the procedure is not used in patients outside of this refined eligible population; reduce the cost of the device; and consistent with ESC advice improve the economic model in terms of structure, time horizon, effect size estimate and consideration of device replacement (Table 1).

Table 1   Requirements for a resubmission

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

4.   Background

This is the first submission (Applicant Developed Assessment Report [ADAR]) for MSAC Application 1595 - Closed loop UAS for moderate to severe OSA.

The Department has since received a related application, MSAC Application 1630 for hypoglossal nerve stimulation using the Genio System for the treatment of moderate to severe obstructive sleep apnoea in patent who have failed or intolerant to continuous positive airways pressure, submitted by Nyxoah S.A.

5.   Prerequisites to implementation of any funding advice

Items on the Australian Register of Therapeutic Goods (ARTG) that are relevant to this application are shown in Table 2.

Table 2   Closed loop UAS devices included on the ARTG

ARTG no.	GMDN	Product name	Product category	Sponsor	Manufacturer
340930 (ARTG start date 6/8/2020)	60360 Implantable sleep apnoea treatment system	Inspire IV Implantable Pulse Generator Model 3028 - Implantable sleep apnoea treatment system	Medical Device Class AIMD	Plexus RA Pty Ltd	Inspire Medical Systems
340931 (ARTG start date 6/8/2020)	60360 Implantable sleep apnoea treatment system	Inspire Stimulation Lead Model 4063 - Implantable sleep apnoea treatment system	Medical Device Class III	Plexus RA Pty Ltd	Inspire Medical Systems
340932 (ARTG start date 6/8/2020)	60360 Implantable sleep apnoea treatment system	Inspire Respiratory Sensing Lead Model 4340 - Implantable sleep apnoea treatment system	Medical Device Class III	Plexus RA Pty Ltd	Inspire Medical Systems
340933 (ARTG start date 6/8/2020)	60360 Implantable sleep apnoea treatment system	Inspire Physician Programmer Model 2740 - Implantable sleep apnoea treatment system	Medical Device Class III	Plexus RA Pty Ltd	Inspire Medical Systems
340934 (ARTG start date 6/8/2020)	60360 Implantable sleep apnoea treatment system	Inspire Sleep Remote Model 2500 - Implantable sleep apnoea treatment system	Medical Device Class III	Plexus RA Pty Ltd	Inspire Medical Systems

Source: Public ARTG summaries of the products, available at the ARTG website; accessed 16 September 2020.
Abbreviations: AIMD=Active implantable medical device; ARTG=Australian register of therapeutic goods; GMDN=Global medical device nomenclature

As per the ARTG listings, the closed loop UAS is indicated to treat moderate to severe OSA ($15\leq$ apnoea–hypopnoea index [AHI] ≥65) in patients who are not effectively treated by, or able to tolerate, positive airway pressure therapies. The Instructions for Use (IFU) supplied with the devices in Australia, a requirement of the device's inclusion on the ARTG, specifies that the closed loop UAS is contraindicated for use in patients with complete concentric collapse (CCC) of the soft palate.

6.   Proposal for public funding

The applicant proposed MBS item descriptors are provided in Table 3, Table 4 and Table 5.

Table 3   Proposed MBS item descriptor

	Category 3 – Therapeutic procedures

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

MBS Fee: $943.00 Benefit 75% = $707.25 (in-hospital/admitted patient only)	

Source: Table 9, p29 of the ADAR.

Table 4   Proposed MBS item descriptor for re-positioning or removal of the implantable pulse generator (IPG) device; ESC proposed changes (strikethrough)

	Category 3 – Therapeutic procedures

MBS item #####
 	
Unilateral closed-loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, surgical repositioning or removal of electrical pulse generator for management of moderate to severe obstructive sleep apnoea ~~in a patient who:~~
 	
  ~~a) has an Apnoea Hypopnoea Index of greater than or equal to 15 and less than or equal to 65; and~~
 	
  ~~b) is aged 18 and over; and~~
 	
  ~~c) has failed or is intolerant to continuous positive airway pressure or bilevel airway pressure; and~~
 	
  ~~d) has a BMI less than or equal to 32 kg/m²; and~~
 	
  ~~e) does not have complete concentric collapse of the upper airway~~
 	
Only once per patient
Multiple Operation Rule
(Anaes.)	

MBS Fee: $161.95 Benefit 75% = $121.50 (in-hospital/admitted patient only)	

Source: Table 10, p29-30 of the ADAR.

Table 5 Proposed MBS item descriptor for replacement of IPG at end of battery life; ESC proposed changes (strikethrough)

Category 3 – Therapeutic procedures
MBS item #####
Unilateral closed loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, surgical replacement of electrical pulse generator~~., for management of moderate to severe obstructive sleep apnoea in a patient who:~~
~~a) has an Apnoea Hypopnoea Index of greater than or equal to 15 and less than or equal to 65; and~~   ~~b) is aged 18 and over; and~~   ~~c) has failed or is intolerant to continuous positive airway pressure or bilevel airway pressure; and~~   ~~d) has a BMI less than or equal to 32 kg/m²; and~~   ~~e) does not have complete concentric collapse of the upper airway~~
~~Only once per patient~~   Multiple Operation Rule
MBS Fee: $346.05 Benefit 75% = $259.55

Source: Table 11 p30 of the ADAR.

The commentary noted that PASC requested:

- The addition of an MBS explanatory note that identified the required expertise and management within a multidisciplinary environment, however this was not provided in the ADAR.
- Clarification of whether 'assistance on operation' need to be added, however this has not been added to the item descriptors and the ADAR has not provided clarification of this matter.
- Advice on how the two cut-offs, failed CPAP and intolerant to CPAP, affected the definition of the patient population for MBS purposes, however this was not provided in the ADAR.

The commentary proposed that it would be informative for the item descriptors to include a definition of CPAP failure and to identify the patients that would be eligible for re-positioning or removal of the IPG device.

The commentary also proposed that the item descriptor in table 4 be amended to include a reason for the IPG removal, i.e. should be modified to state 'Unilateral closed loop hypoglossal nerve stimulation therapy through stimulation of the hypoglossal nerve, surgical replacement of electrical pulse generator *when battery has been depleted*, for management of moderate to severe obstructive sleep apnoea in a patient who:'.

The commentary noted that the ADAR indicated that did not discuss the accuracy of identifying patients without CCC, but indicated this would be done using drug induced sleep endoscopy (DISE).

7. Summary of public consultation feedback/consumer issues

Consultation feedback was received from one individual specialist and two specialist organisations. The responses were in support of MBS listing of closed loop UAS in the proposed MBS population noting the symptomatic benefit that closed loop UAS may provide to the patients who are unable to tolerate or unsuitable for other forms of therapy for OSA, along with reducing the burden of untreated OSA (e.g. cardiovascular consequences). There was also strong consensus among the responses that appropriate patient selection co-ordinated by a multi-disciplinary team and appropriate clinician training/credentialing is

necessary. Two of the response also noted that there are other devices that can provide hypoglossal nerve stimulation therapy that are intended to be used in the same patient population.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

Closed loop UAS includes the surgical placement of an IPG, a respiratory sensing lead and a stimulation lead that delivers mild stimulation to the hypoglossal nerve. The closed loop UAS is designed to increase the volume of the airways during sleep, by applying stimulation to the hypoglossal nerve which innervates the extrinsic and intrinsic muscles of the tongue, causing tongue protrusion and stiffening of the anterior pharyngeal wall. The ADAR indicated that the hypoglossal nerve does not have a sensory function and is purely motor. The hypoglossal nerve has the ability to affect multiple levels of the pharyngeal airway rather than the tongue base alone.

Description of Medical Condition(s)

OSA is a disorder of sleep, characterised by repeated upper airway obstructions during the night, with resultant oxygen desaturations and arousals. An apnoea is defined as a complete cessation of breathing that lasts 10 seconds or longer. The diagnosis of OSA is confirmed by conducting a polysomnography (PSG) sleep study to observe the number of apnoea and/or hypopnea episodes per hour (the AHI), with moderate to severe OSA defined as having an AHI ≥ 15 and ≤ 65.

The population proposed for treatment with closed loop UAS is patients who:

- are 18 years or older with a body mass index (BMI) less than or equal to 32 kg/m²,
- have moderate to severe OSA, defined as having an AHI ≥ 15 and ≤ 65,
- have been confirmed to have failed or cannot tolerate CPAP or bi-level positive airway pressure (BIPAP), and
- do not have total concentric collapse at the level of the soft palate.

In the ratified PICO Confirmation for MSAC application 1595, failure of CPAP therapy was defined as continued AHI >20 despite appropriate CPAP usage, and CPAP intolerance was defined as:

1. inability to use CPAP (>5 nights per week of usage: usage defined as >4 hours of use per night), or
2. unwillingness to use CPAP (for example, a patient returns the CPAP system after attempting to use it).

The current and proposed clinical management algorithm for the treatment of patients with moderate to severe OSA, are presented in Figure 1 and Figure 2.

The ADAR indicated that the proposed clinical management algorithm is similar to the current algorithm, although following implantation it is unlikely that CPAP would be resumed, as may happen following upper airway surgery.
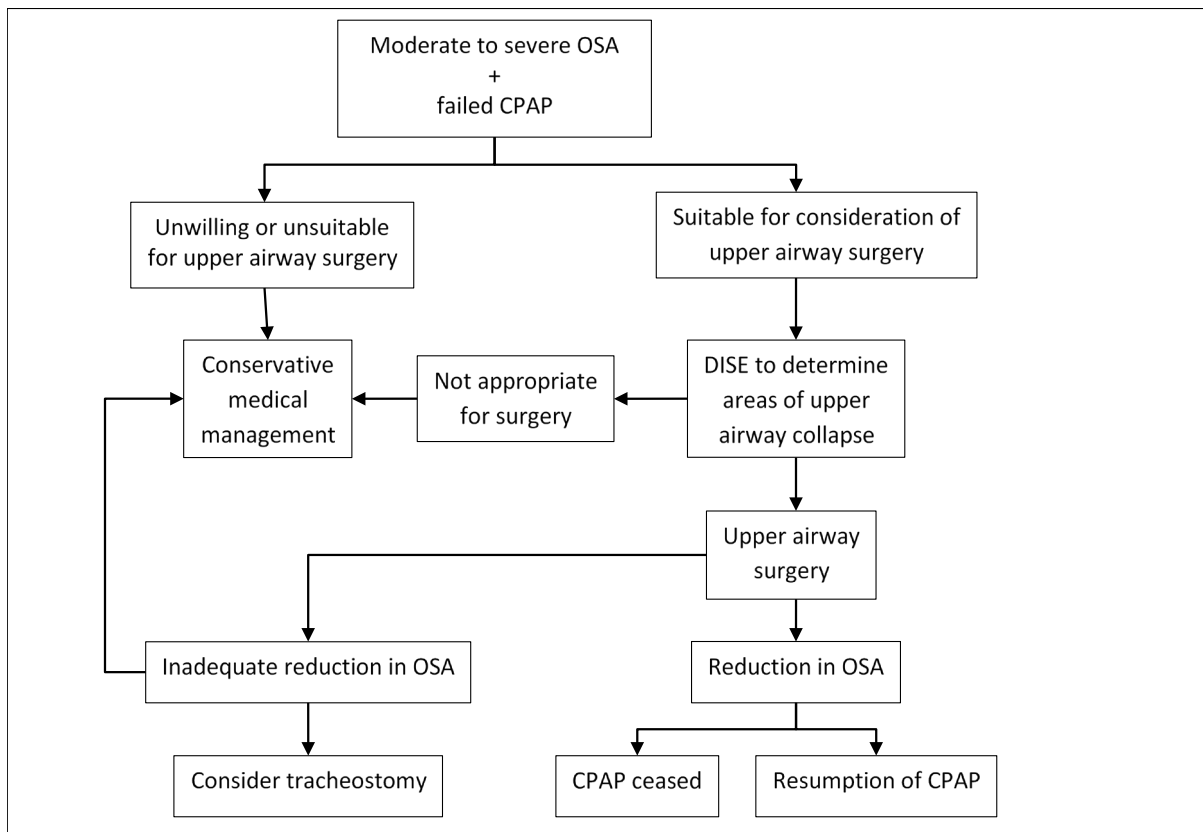
Figure 1 Current clinical management algorithm for moderate to severe OSA
Source: Figure 8, p42 of the ADAR.
Abbreviations: CPAP=continued positive airway pressure; DISE=drug induced sleep endoscopy; OSA=obstructive sleep apnoea
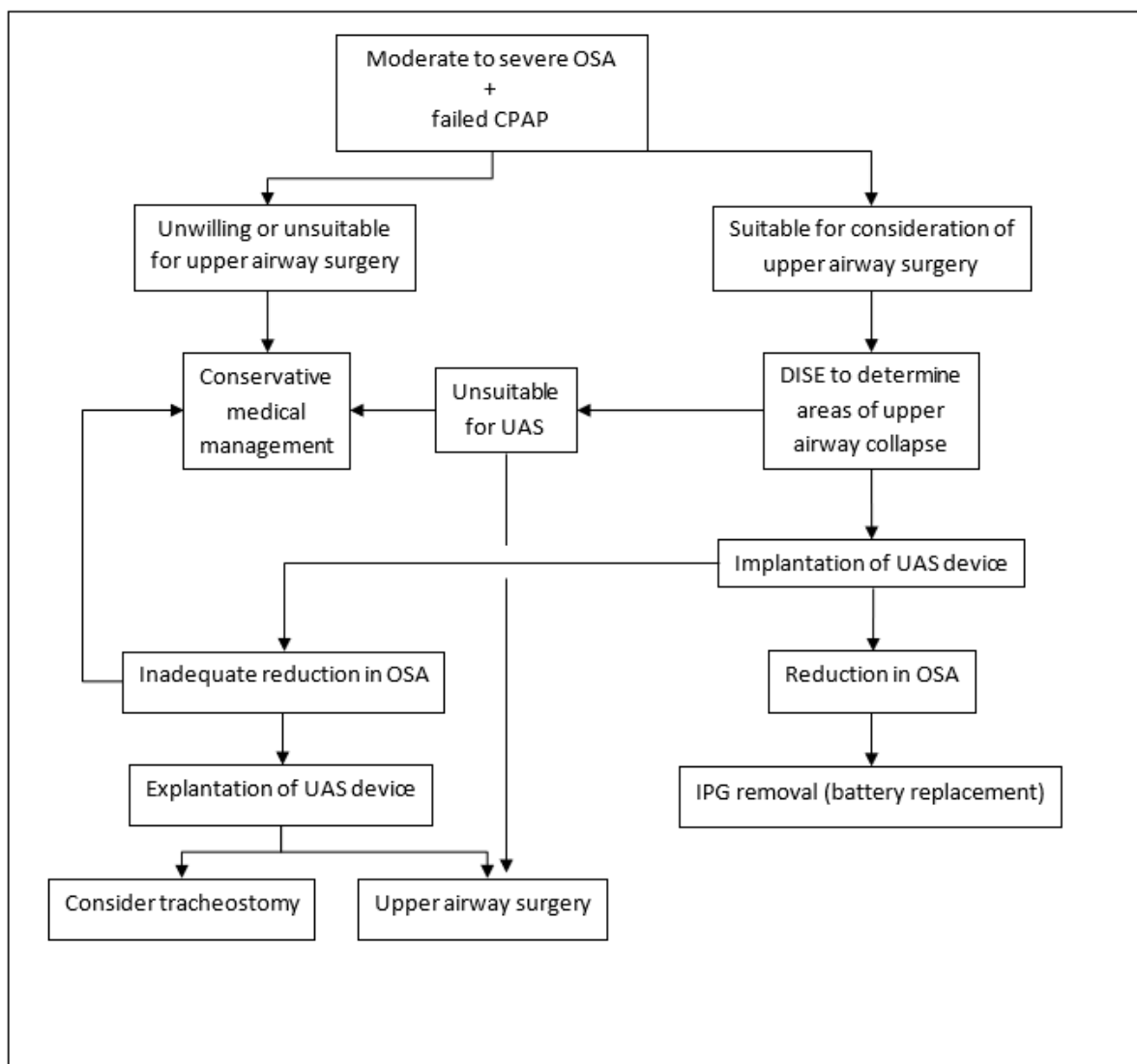
Figure 2 Proposed clinical management algorithm for moderate to severe OSA
Source: Figure 9, p43 of the ADAR.
Abbreviations: CPAP=continued positive airway pressure; DISE=drug induced sleep endoscopy; IPG=implantable pulse generator; OSA=obstructive sleep apnoea; UAS=upper airway stimulation

The commentary noted that the ADAR provided no discussion of whether closed loop UAS would replace other upper airway surgery, such as uvulopalatopharyngoplasty (UPPP) (supplementary comparator), or would sit alongside such therapy in the clinical management algorithm. Nor did the ADAR provide discussion around the possibility that UPPP may occur prior to or following UAS. Using expert opinion, the ADAR assumed that closed loop UAS would substitute for UPPP (30%), however the ADAR provided no evidence for the supplementary comparator of UPPP, so there is no evidence upon which to base the replacement of UPPP with closed loop UAS. Overall, the commentary considered that the ADAR did not adequately describe the clinical management algorithm.

9. Comparator

Medical management strategies (main comparator)

The proposed comparator is conservative medical management, termed medical management strategies (MMS), which may include: weight and alcohol reduction; sleep positioning therapy; sleep hygiene education; and use of mandibular advancement appliances.

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Upper airway surgery (supplementary comparator)

Upper airway surgery, such as UPPP, was nominated as a supplementary comparator. The ADAR noted there are a number of surgical options for treating moderate to severe OSA which included: UPPP, Radiofrequency Volumetric Tissue Reduction (RFVTR), genioglossus advancement, hyoid suspension, midline glossectomy and lingualplasty, laser assisted uvuloplasty, maxillomandibular osteotomy (MMO) and maxillomandibular advancement (MMA). The ADAR noted that the following MBS items may be relevant for upper airway surgery to treat OSA: MBS item 41786 (UPPP), MBS item 30272 (partial excision of the tongue), MBS item 41779 (pharyngotomy) and MBS item 41787 (uvulectomy and partial palatectomy).

While the ADAR nominated upper airway surgery as a supplementary comparator, the comparative safety, efficacy and cost-effectiveness of closed loop UAS *vs*. UPPP was not presented in the ADAR. Rather the ADAR claimed that a comparison between UAS and UPPP was not possible given differences in patient populations in the available evidence for each intervention.

10. Comparative safety

The clinical evidence presented in the ADAR consisted of one single arm interventional study (STAR[2] study), reported in three publications (Woodson 2018[3], Strollo 2017[4] and Strollo 2014[5]) with an embedded randomised withdrawal study (Woodson 2014[6]), summarised in Table 6.

The ADAR also identified the SKUP3[7] study (Browaldh 2018[8], Joar 2018[9]) as evidence for the supplementary comparator UPPP. However, the ADAR claimed the SKUP trial had substantial differences to the STAR study, and therefore claimed a comparison of closed loop UAS and UPPP surgery could not be made. The commentary considered this was reasonable.

Table 6 Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Key outcomes	Result used in economic model
Woodson 2018 STAR study	126	Coh, MC 5 years	High	Moderate to severe OSA; intolerant to CPAP	AHI, ODI, ESS, FOSQ, adverse events	Used
Woodson 2014 STAR sub-study	46	R, MC 1 week therapy withdrawal; assessment at 6 months	High	Moderate to severe OSA; intolerant to CPAP – responders to treatment	AHI, ODI, ESS, FOSQ	Not used

Source: Table 22, p56 of the ADAR
Abbreviations: AHI=apnoea hypopnoea index; CPAP=continuous positive airway pressure; Coh=cohort; ESS=Epworth Sleepiness Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; MC=multi-centre; ODI=oxygen desaturation index; OSA=obstructive sleep apnoea;

[2] Stimulation therapy for apnoea reduction (STAR), NCTC 01161420
[3] Woodson, B.T. et al. (2018). Otolaryngology - Head and Neck Surgery, 159: 194-202.
[4] Strollo, J. R. et al. (2017). Sleep, 40: A209.
[5] Strollo, J. R. et al. (2014). New England Journal of Medicine, 370: 139-149.
[6] Woodson, B.T. et al. (2014). Otolaryngology - Head and Neck Surgery, 151: 880-887.
[7] RCT of the effect of uvulopalatopharyngoplasty compared to expectancy in patients with obstructive sleep apnoea (SKUP3), NCTC 01659671
[8] Browaldh, N. et al. (2018). Laryngoscope, 128: 1238-1244.
[9] Joar, S. et al. (2018). Sleep, 41.

R=randomised; SB=single blind.

The commentary considered the quality of evidence to be low for the following reasons:

- The main study (Woodson 2018; Strollo 2014) had a high risk of bias, and even though the *post hoc* withdrawal sub-study among UAS 'responders' was randomised, patients were aware that therapy was withdrawn for one week, and these patients then re-commenced treatment.
- The ADAR did not present comparative results from the STAR study assessing change from baseline to 12 months in AHI, oxygen desaturation index (ODI), Functional Outcomes of Sleep Questionnaire (FOSQ) and Epworth Sleepiness Scale (ESS).
- While there was considerable follow-up in the main study (5 years), there were no statistical comparisons provided of change from baseline values in AHI, ODI, FOSQ and ESS.
- While there were 126 patients enrolled in the STAR study, and 97 completed 5 years of follow-up (77%), only 71 had a PSG at the 5 year time point (56%). With close to half of the patients not being assessed by PSG at the 5 year time point, this raises questions about the assessment of the longer-term safety and effectiveness of the device.

Furthermore, the commentary considered that the ADAR literature searches were not satisfactory. While the searches identified the key safety and effectiveness studies, the commentary noted that 10 relevant papers were not identified by the ADAR and 2 papers were excluded that should not have been excluded. However, in the pre-ESC response, the applicant considered that none of these studies were suitable for inclusion.

Closed loop UAS vs. Medical management strategies

There were no comparative safety results available, as the STAR study was a single arm interventional study in which all patients were treated with closed loop UAS therapy. The ADAR stated that all adverse events (AEs) occurred following the intervention. The number of events and number and proportion of patients with AEs sourced from the Strollo (2014) publication, summarising AEs at the 12 month time point of the STAR study are provided Table 7. The commentary noted that the ADAR did not indicate if an attempt was made to find any published data reporting AEs in MMS patients.

Table 7   Summary of adverse events at 12 months in the STAR study (patients treated with UAS)

Adverse event	Closed loop UAS (N=126)	
	Number of events	Number of patients with event
Serious AE	35	27 (21%)
Device – revision	2	2 (2%)
Death, unrelated	2	2 (2%)
Other unrelated[a]	31	23 (18%)
Procedure-related non-serious AE	165	72 (57%)
Post-op discomfort related to incisions	46	33 (26%)
Post-op discomfort not related to incisions	39	31 (25%)
Temporary tongue weakness	35	23 (18%)
Intubation effects	18	15 (12%)
Headache	8	8 (6%)
Other post-op symptoms	22	14 (11%)
Mild infection	1	1 (1%)
Device-related non-serious AE	190	85 (67%)
Discomfort due to electrical stimulation	80	50 (40%)
Tongue abrasion	33	26 (21%)
Dry mouth	13	13 (10%)
Mechanical pain associated with device presence	8	8 (6%)
Temporary internal device functionality complaint	14	12 (10%)
Temporary internal device usability or functionality complaint	8	7 (6%)
Other acute symptoms	25	19 (15%)
Mild or moderate infection (skin cellulitis)	1	1 (1%)

Source: Table 23, p59 of the ADAR.
Abbreviations: AE=adverse event; UAS=upper airway stimulation
[a] Included cardiac conditions or coronary artery disease or arrhythmias or chest pain (N=8), accidents or injuries (N=11), other surgeries (N=12)

The ADAR stated that two patients experienced serious device-related AEs requiring re-positioning of the device. The remaining 33 serious AEs were not considered to be related to the implant procedure, and the majority occurred within 30 days of the surgery and were expected post-surgical events. The ADAR noted that by the 5 year time point, three patients had their devices explanted; two non-responding patients had elective device removal and one patient had a non-elective removal due to an unrelated medical condition.

The commentary noted that a systematic review by Certal (2015)[10], which was not included in the ADAR, reported that of the 200 patients included in the review, nine (4.5%) had serious device-related AEs that led to removal of the device. Although not mentioned by the ADAR, in the STAR study 40% of patients (N=50) reported discomfort due to electrical stimulation, which increased to 60.3% of patients at the 5-year timepoint. This would suggest discomfort impacted an increasing number of patients over time, and also indicates there is potential for discomfort in a considerable proportion of patients. In the pre-ESC response, the applicant considered Certal (2015) was not suitable for inclusion as it included non-closed loop UAS.

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[10] Certal, V.F. et al. (2014). Laryngoscope, 125:1254-1264.

Overall, the commentary considered that there was very limited AE data presented by the ADAR and the information provided did not allow for a comparison of closed loop UAS and the main comparator MMS. The safety claim made by the ADAR (inferior safety compared to MMS), while not supported by the evidence presented, may be reasonable given that it would be expected that surgical implantation of a device that creates discomfort in patients would have inferior safety to medical management strategies.

11.   Comparative effectiveness

The ADAR reported that the pre-specified definition of response in the STAR study was a reduction in AHI of at least 50% from baseline and an AHI score of less than 20. At 5 years the response rate was estimated to be 65% at 1 year (Woodson 2018). This was maintained with a response rate of 63% at 5 years. Similarly, ESS and FOSQ scores were claimed to have improved significantly from baseline and maintained at 5 years. During the RCT withdrawal study, AHI, ODI ESS and FOSQ returned to baseline levels following withdrawal of therapy.

The balance of clinical benefits and harms of closed loop UAS vs. MMS, as presented by the ADAR, are shown in Table 8.

Table 8 Balance of clinical benefits and harms of closed loop UAS relative to medical management, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)[a]	Mean+/-SD (95% CI) P value (where available	Comments
Change AHI at 5 years	1 Single arm interventional trial. Subjects serve as own control N=126	Downgraded for pre-post trial design. ⊕⊕⊕⊙	-17.1+/-1.7 (-20.5 to -13.6)	
Change FOSQ	1 Single arm interventional trial. Subjects serve as own control	Downgraded for pre-post trial design. ⊕⊕⊕⊙	3.2+/-0.3 (CI 2.6 to 3.8)	Participants unable to be blinded to intervention
Change ESS	1 Single arm interventional trial. Subjects serve as own control N=126	Downgraded for pre-post trial design. ⊕⊕⊕⊙	-4.3 +/- 0.6 (CI – 5.4 to -3.2)	Participants unable to be blinded to intervention
AHI Difference	I study RCT therapy withdrawal trial N=46	Downgraded lack of reporting of method of randomisation (PSG assessment blinded) ⊕⊕⊕⊙	-16.9 (-24.7,-9.0) <0.001	
ODI Difference	I study RCT therapy withdrawal trial N=46	Downgraded lack of reporting of method of randomisation (PSG assessment blinded) ⊕⊕⊕⊙	-15.1 (-22.7,-7.5) p<0.001	
Difference FOSQ	I study RCT therapy withdrawal trial N=46	Downgraded not possible to blind subjects ⊕⊕⊙⊙	2.9 (0.8, 5.0) (0.8,5.0) P=0.008	Participants unable to be blinded to intervention
Difference ESS	I study RCT therapy withdrawal trial N=46	Downgraded not possible to blind subjects ⊕⊕⊙⊙	-4.5 (-7.5, -1.4) P =0.5	Participants unable to be blinded to intervention

[a] GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. SD=standard deviation; CI= 95% Confidence Interval

AHI: Apnoea hypopnoea index, ODI: Oxygen Desaturation Index, FOSQ: Functional Outcomes of Sleep Questionnaire, ESS: Epworth Sleepiness Scale

The commentary raised a number of concerns with the comparative evidence presented by the ADAR:

- The baseline values in the STAR study were assumed in the ADAR to be representative of MMS therapy. However, the ADAR did not provide any evidence to support this assumption, as such the evidence presented cannot be considered to provide a comparison with MMS.

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- To account for missing values, the ADAR used multiple imputation. It was reported that 97 patients (77%) completed 5 years of follow-up, although only 71 had a PSG at the 5 year time point (56%). However, there was no information provided regarding missing data for the individual outcomes at each time point.
- The STAR study did not assess statistical significance of the observed changes and the ADAR did not provide any discussion of the clinical significance of these changes.
- In the STAR study, response was defined as a reduction of at least 50% from baseline and AHI <20, and the response rate at 5yrs was estimated to be 63% following last observation carried forward (LOCF) analysis, which was similar to the response rate at 12 months, which was 65%. The commentary noted that it is possible that carrying forward the last response will favour UAS. In addition, a response rate of 65% at 12 months and 63% at 5 years means that a considerable proportion of the population did not meet the response criteria.

The commentary also noted that Strollo (2014) provided the results of the STAR study at 12 months, the change from baseline values were presented as means, standard deviations, medians and interquartile ranges. Strollo (2014) stated these values were presented because some variables, such as the 12 month scores on the AHI and the ODI showed evidence of non-normality.

Further, although not mentioned by the ADAR, Strollo (2014) noted that in the non-responders, there were a total of 19 patients (15%) who showed an increase in AHI following device activation. Of these 19 patients, the increase in AHI was >15 in 7 patients, and <15 in the remaining 12 patients. In addition, there were 4 patients with an increase of AHI >60 at 12 months. The commentary concluded that the available data demonstrated that while some patients showed improvement in AHI, there were others that showed a worsening.

Table 9 Results of the STAR study at 5 years – change from baseline

| Outcome[a] | STAR (N=126) | | | | | | Change from baseline[b] |
| | Baseline | | 12 Months | | 36 Months | 60 Months | Mean (95% CI) |
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Mean (SD)	
AHI	32 (11.8)	29.3	15.3 (16.1)	9.0	11.5 (14.0)	12.4 (16.3)	-17.1 (-20.5, 13.6)
ODI	28.9 (18.2)	25.4	14.0 (15.6)	7.4	9.1 (11.7)	9.9 (14.5)	NR
FOSQ	14.3 (3.2)	14.6	17.3 (2.9)	18.2	17.4 (3.5)	18.0 (2.2)	3.2 (2.6, 3.8)
ESS	11.6 (5.0)		7.0 (4.3)	6.0	7.0 (5.0)	6.9 (-4.7)	-4.3 (-5.4, -3.2)

Source: Table 8, pxx of the commentary
Abbreviations: AHI=apnoea hypopnoea index; CI=confidence interval; ESS=Epworth Sleepiness Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; NR=not reported; ODI=oxygen desaturation index; SD=standard deviation
[a] An improved outcome was indicated by lower values for the AHI, ODI and ESS scales and a higher value for the FOSQ
[b] Multiple imputation was used to account for missing values.

Clinical claim

On the basis of the benefits and harms reported in the evidence base, the ADAR proposed that, relative to medical management, closed loop UAS has inferior safety and superior effectiveness.

However, the commentary considered that the available evidence, including that not presented by the ADAR, did not support the ADAR's clinical claim for the following reasons:

- There was no comparative safety evidence presented, hence it cannot be concluded that closed loop UAS has inferior safety to MMS. However, it may be reasonable to expect that surgical implantation of a device would have inferior safety to medical management strategies. In addition, along with potential risk associated with surgery, evidence from the STAR study indicated that between 40% and 60% of patients experienced discomfort with the device.

- The ADAR did not provide evidence to support its claim that the baseline values in the STAR study represented medical management. As such, the evidence presented does not demonstrate superior effectiveness of closed loop UAS over MMS.

- While the evidence from the STAR study showed there were improvements in the AHI, ODI, FOSQ and ESS outcomes for patients with the closed loop UAS implant, there was limited evidence presented to demonstrate that these changes represented a clinical benefit, or the potential magnitude of the benefit. While the ADAR identified a MCID value for AHI, the identified value (change of 5 events/hour) could not be validated, and the ADAR provided no discussion of the potential magnitude of benefit. In the pre-ESC response, the applicant highlighted that the improvement in ESS of 4.6 points is twice the MCID reported in Crook (2018)[11], in patients with mild to severe OSA.

- The ADAR did not address the non-normality of AHI and ODI data at 12 months, as noted by Strollo (2014). In the pre-ESC response, the applicant considered since mean ESS was used in the model and there is a linear relationship of ESS to utility as per published equation[12], there would be no impact to model results.

- While the withdrawal sub-study of the STAR study showed that response decreased when therapy was withdrawn, it may be reasonable to expect such a response with therapy withdrawal and it is not clear how this demonstrates that closed loop UAS is superior to MMS.

The commentary also raised that patients with moderate to severe OSA are at risk of cardiovascular complications (Strollo 2014). However, the STAR study did not assess cardiac event outcomes, and as such, the available evidence does not provide any indication of a cardiac or mortality benefit for these patients.

12.   Economic evaluation

Based on the ADAR clinical claim that closed loop UAS has inferior safety and superior effectiveness compared to MMS, the ADAR presented a cost-utility analysis comparing closed loop UAS with MMS.

The economic evaluation is summarised in Table 10.

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[11] Crook, S. et al. (2018). Thorax, 74(4):390-396
[12] EQ-5D utility = baseline ESS score * -0.01) + 0.893

Table 9 Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator	MMS (medical management strategies)
Type of economic evaluation	Cost-utility analysis
Sources of evidence	STAR study; McDaid (2009); Young (2008)
Time horizon	45 years (lifetime)
Outcomes	LYG and QALYs
Methods used to generate results	Markov model
Health states	On treatment, off treatment and death
Cycle length	12 months
Discount rate	5%
Software packages used	Excel 2016

Source: Table 32, p74 of the ADAR.
Abbreviations: LYG= Life Years Gained; QALY=Quality-adjusted life year

The commentary considered that the model was not informative due to the following limitations/issues identified:

- There is limited support for the claimed superiority of closed loop UAS, given the lack of justification provided for the use of baseline STAR study values as representative of MMS values, and the lack of evidence that the observed changes in the STAR study represented a clinical benefit, or the magnitude of the benefit. In the pre-ESC response, the applicant acknowledged the limitations of this approach, but considered it is the most realistic estimation of treatment outcomes of medical management in this population.

- The applicability of the STAR study to the proposed MBS patient population is unclear. The commentary noted that the AHI values of patients included in the STAR study range from just less than 20 to 60, and that Strollo (2014) indicated that patients with AHI <20 and >50 were excluded. Given the above, it is likely that the patient population in the STAR study is only a subset of the proposed population in regard to the AHI criterion. In addition, the STAR study included close to 20% of patients who had already had surgery with UPPP, and it is not clear how applicable this patient population is to the proposed MBS population.

- The ADAR did not adequately justify the model structure. The health states of 'on' and 'off' treatment, and comparing UAS (treatment) with MMS, appeared to conflate health states and treatment. Patients in the 'off treatment' arm of the model cannot enter the 'on treatment' arm, and even though the ADAR stated that patients in the 'on treatment' state (ie those treated with UAS) may have the device explanted and move to the 'off treatment' health state, the results for these 'off treatment' patients are applied only to the UAS arm of the model, ie treated patients. The ADAR has not explained why health states which cannot be entered by both arms of the model were used.

- The method used to determine utility values was not adequately justified by the ADAR, and the model set-up does not allow for assessment of alternate, literature-based utility values. In the published economic models of UAS (Pietzsch 2015; Pietzsch 2017), the utility values were literature-based, the baseline utility decreased with age, and the model structures included cardiovascular health states. However, the ADAR model used the baseline ESS score from the STAR study (11.6) to determine the 'off-treatment' utility value, and the 12 month ESS score (7.0) to determine the 'on treatment' utility value. The model assumed that ESS results observed at 5 years would be maintained for 45 years, for which there is no validation. This assumption

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was not adequately justified (Table 11). In the pre-ESC response, the applicant considered that it was conservative to exclude a decrement for ESS for MMS as without treatment, quality of life will worsen over time. The applicant considered the reduction in ESS in control arm is supported by the recent study (Mehra et al 2020[13]), and the inclusion thereof would reduce the ICER to $**redacted** (from base case of $**redacted**).

- The ADAR model assumed a survival benefit for UAS, however mortality was sourced from a study with limited applicability (Young 2008; with 9.5% of patients with moderate to severe OSA and included patients with AHI score ≥65 up to 97 in severe category compared with AHI ≥15 and ≤65 in proposed population), and there was no demonstration of a relationship between UAS and mortality.

- The ADAR claimed that assuming no difference in cardiovascular events between on treatment and off treatment patients is conservative. However, the ADAR has not appropriately justified why cardiovascular events were not considered as health states (as in published models), or why cardiovascular outcomes were not included as model outcomes. In the pre-MSAC response, the applicant highlighted cardiovascular outcomes were not included as they were not measured in the STAR study; to include cardiovascular outcomes would have required multiple assumptions, considerably increasing the uncertainty.

Table 10 Assumptions applied in the model

Model component	Assumption/data	Comment
ESS data	ESS scores from baseline of the STAR study were used for 'off treatment' patients, and ESS scores at 12 months of the STAR study were used for 'on treatment' patients.	ESS scores were transformed to determine utility values. This only applies to UAS patients, as there were no QALYs applied for 'on treatment' patients in the MMS group. This illustrates the lack of clarity associated with the use of treatment status as health states.
Explantation of UAS device	Movement from 'on treatment' to 'off treatment' for patients implanted with the closed loop UAS only occurs in the first cycle of the model. Data from the STAR study showed 3 of 126 patients had the device explanted.	This was reasonable.
MMS patients	All MMS patients enter the model in the 'off treatment' health state and remain in this state until they die.	MMS patients are not treated with closed loop UAS so they are by definition 'off treatment'. It is not clear why a health state was created for this.
Change over time	The model assumed no disease progression or deterioration in quality of life for 'on treatment' and 'off treatment' patients.	This was an assumption not supported by evidence, as the STAR study provided data to only 5 years, and there was no evidence provided to assume the same results will apply for a further 40 years.
Cardiovascular events	The model assumed there is no difference in cardiovascular events between the 'on treatment' and 'off treatment' health states.	This is not likely to reflect treatment with UAS as compared to MMS, as a key characteristic for OSA is the occurrence of cardiovascular events, as stated by the ADAR (p80).

Source: Table 11, pxxiv of the commentary
Abbreviations: ESS=Epworth Sleepiness Scale; MMS=medical management strategies; OSA=obstructive sleep apnoea; UAS=upper airway stimulation

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

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the base case assumptions, are presented in Table 12. However, the commentary considered that the model results are not likely to accurately reflect the cost-effectiveness of closed loop UAS.

Table 11 Results of the modelled evaluation

	Closed loop UAS	MMS	Increment
Cost	$redacted	$redacted	$redacted
LYs	14.37	12.52	1.84
QALYs	11.83	9.77	2.07
Incremental cost/LY gained			$redacted
Incremental cost/QALY gained			**$redacted**

Source: Table 43 and Table 44, p87 of the ADAR.
LYs=life years; MMS=medical management strategies; QALYs=quality adjusted life years; UAS=upper airway stimulation

The ADAR claimed the modelled results were most sensitive to mortality ratios for 'on treatment' and 'off treatment' patients, the regression equation to transform ESS to EQ-5D utilities and the battery life of the closed loop UAS System (Figure 3).

Figure 3 Key drivers of economic model - redacted

However, the commentary considered that the sensitivity analysis results presented by the ADAR should be interpreted with caution, given the concerns with the overly simplified model structure (health states comprised of treatment) and parameter values (utility values, mortality). The commentary also noted that the results of the sensitivity analyses showed the model was sensitive to the time horizon and the hazard ratio applied to mortality. Shortening the time horizon to 15 years (which would allow one replacement UAS to be implanted), increased the incremental cost-effectiveness ratio (ICER)/quality-adjusted life year (QALY) by 111%, to $**redacted**. Altering both model duration (to 15 years) and mortality hazard ratios for both 'on treatment' and 'off treatment' (20% decrease) increased the ICER/QALY by 130% to $**redacted**.

The key drivers of the model are summarised in Table 13.

Table 12 Key drivers of the economic model

Description	Method/Value	Impact
Model structure	'On' and 'off' treatment health states comparing UAS (treatment) with medical management (MMS), appears to conflate health states and treatment.	High, unable to test impact
Time horizon	Lifetime (45 years). With a starting age of 54.5 years, model duration seems excessively long.	High, favours UAS
Mortality hazard ratio	Derived from Young (2008) and applied to general population mortality. Derivation of hazard ratios was based on categorisation of patients that did not match the requested item descriptor	High, favours UAS
ESS scores	ESS scores determine utility value and are assumed to remain the same over the 45 year model time horizon. The equation used to derive utility values is based on an unavailable 1992 abstract and has not been validated. In. addition, no justification that ESS scores would remain the same over 45 years was provided.	Moderate, favours UAS

Source: Table 13, pxxvi of the commentary
Abbreviations: ESS=Epworth Sleepiness Scale; UAS=upper airway stimulation

The pre-MSAC response presented additional multivariate sensitivity analyses (Table 14) which varied the mortality HRs taken from Young 2008 and Marshall 2008, and also

including analyses where mortality HRs were reverse calculated so that incremental QALYs in the model are equal to those in Pietzsch 2015 (which included cardiovascular outcomes), and with an alternative time horizon of 20 years.

Table 13 Additional sensitivity analysis provided in the pre-MSAC response

Sensitivity analyses	Incremental costs	Incremental QALY	ICER per QALY
Base case	$redacted	2.07	$redacted
Univariate Analysis			
Time horizon: 20 years (base case:45 years)	$redacted	1.19	$redacted
Mortality HR for 'Patients Off Treatment: 1.67* (base case: 3.0)	$redacted	0.83	$redacted
Mortality HR for 'Patients Off Treatment: 1.9** (base case: 3.0)	$redacted	1.09	$redacted
Mortality HR for 'Patients Off Treatment: 2.2*** (base case: 3.0)	$redacted	1.39	$redacted
Mortality HR for 'Patients Off Treatment: 4.4**** (base case: 3.0)	$redacted	2.97	$redacted
Increased the ESS by 1.8 from Year 2 onwards in the MMS arm	$redacted	2.27	$redacted
Multivariate analyses			
Time horizon: 20 years, Mortality HR for 'Patients Off Treatment: 1.67	$redacted	0.60	$redacted
Time horizon: 20 years, Mortality HR for 'Patients Off Treatment: 1.9	$redacted	0.71	$redacted
Time horizon: 20 years, Mortality HR for 'Patients Off Treatment: 2.2	$redacted	0.85	$redacted
Time horizon: 45 years, PLUS Mortality HR for 'Patients Off Treatment: 4.40 Increased the ESS by 1.8 from Year 2 onwards in the MMS arm	$redacted	3.15	$redacted

Source: Table 1 of the pre-MSAC response
Abbreviations: ESS=Epworth Sleepiness Scale; ICER = incremental cost effectiveness ratio; HR= Hazard ratio; MMS= Medical management strategies; QALY = quality adjusted life year
*HR of 1.67 was estimated such that life-time incremental QALYs become same as reported in Pietzsch 2015 study at 3% discount rate
**HR of 1.90 was estimated such that incremental QALYs at 10-year time horizon become same as reported in Pietzsch 2015 study at 3% discount rate
***HR of 2.2 was estimated using average HRs of severe (HR=3.0) and moderate (HR=1.4) categories reported in Young 2008 study (Table 3)
****HR of 4.4 was sourced from Marshall 2008 study (Table 3-Partially adjusted HR for moderate to severe sleep apnea)

13.   Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of closed loop UAS for treatment of patients with moderate to severe OSA who have failed or are intolerant to CPAP (Table 15). While the ADAR estimated 20,091 patients would be eligible, it was estimated that only 24-150 patients would be treated per year based on availability of qualified surgeons and appropriate surgical centres. Using expert opinion, the ADAR assumed that closed loop UAS would substitute for UPPP in 30% of cases.

Table 14 Estimated cost to the MBS for the listing of closed loop UAS

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients/services	24	40	56	100	150
Total MBS cost	$30,386	$52,454	$75,727	$135,658	$206,503
Substituted MBS services					
UPPP MBS costs	-$5,524	-$9,453	-$13,392	-$23,633	-$36,449
Specialist visits MBS costs	-$1,810	-$3,016	-$4,222	-$16,588	-$27,898
Total substituted MBS services	-$7,324	-$12,469	-$17,614	-$31,173	-$46,759
Net MBS cost	**$23,063**	**$39,985**	**$58,113**	**$104,486**	**$159,745**

Source: Table 59, p99 of the ADAR.
Abbreviations: MBS=Medicare Benefit Schedule; UAS=upper airway stimulation; UPPP=uvulopalatopharyngoplasty

The ADAR estimated net cost to the MBS is $23,063 in Year 1, increasing to $159,745 in Year 5, a total of $385,391 over the first 5 years of listing.

The estimated overall net costs, including device cost (to be covered by PLAC, if listed) and hospital cost, over the first 5 years of listing is $15.3M (Table 16).

Table 15 Estimated total costs for the listing of closed loop UAS

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients/services	24	40	56	100	150
Device cost	$redacted	$redacted	$redacted	$redacted	$redacted
MBS costs					
Implantation of closed loop UAS system	$16,974	$28,290	$39,606	$70,725	$106,088
Surgical repositioning or removal of IPG	$70	$117	$163	$292	$437
Programming closed loop UAS system	$1,810	$3,016	$4,222	$7,540	$11,310
Sub-total	$18,854	$31,423	$43,992	$78,557	$117,835
DISE	$4,680	$7,799	$10,919	$19,499	$29,248
Anaesthesia	$5,428	$9,046	$12,664	$22,615	$33,923
Post-op x rays	$1,426	$2,376	$3,326	$5,940	$8,910
Sub-total	$11,533	$19,221	$26,910	$48,054	$72,080
Specialist visits-ongoing after Year 1	$0	$1,810	$4,826	$9,048	$16,588
Total MBS cost	$30,386	$52,454	$75,727	$135,658	$206,503
Hospitalisation costs					
Implantation of closed loop UAS system	$127,575	$212,625	$297,675	$531,563	$797,345
Surgical repositioning or removal of IPG	$2,506	$4,177	$5,848	$10,443	
Total hospital cost	$130,081	$216,802	$303,523	$542,006	$813,009
Total costs (device, MBS, hospital)	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Substituted services					
UPPP	*-$5,524*	-$9,453	-$13,392	-$23,633	*-$36,449*
Specialist visits	-$1,810	-$3,016	-$4,222	-$16,588	-$27,898
Hospital	-$37,209	-$63,788	-$90,366	-$159,469	-$239,204
Total substituted services	-$44,533	-$76,257	-$107,980	-$190,642	-$285,962
Overall net cost	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

Source: Table 66, p119 of the commentary.
Abbreviations: DISE=drug induced sleep endoscopy; IPG=implantable pulse generator; MBS=medicare benefit schedule; UAS=upper airway stimulation; UPPP=uvulopalatopharyngoplastyItalicised represents numerical corrections made by Department

The commentary noted that the estimated costs are dependent on the claimed limitations of usage due to access (i.e. limited specialists and limited centres performing the procedure), and considered the estimated usage of closed loop UAS to be considerably low, particularly given the size of the estimated eligible patient population. The treatment of 24 patients in the first year of listing represents 0.1% of the eligible population (N=20,091), and the treatment of 150 patients in the fifth year of listing represents 0.7% of the eligible population. Overall, the commentary considered the estimated number of patients likely to use closed loop UAS to be uncertain, as the ADAR did not provide adequate justification for the estimated low usage of UAS nor the estimated number of possible treatment centres. As such, there may be potential for greater usage.

Sensitivity analyses were conducted to explore the impact of increasing and decreasing the number of patients treated per centre, as well as analyses where the rate of substitution of UPPP is altered (Table 17). These results demonstrate that assumed centre numbers and patients per centre are key determinants of estimated net cost.

Table 16 Sensitivity analyses of estimated net cost to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients/services (base case)	24	40	56	100	150
Net MBS cost (base case)	$23,063	$39,985	$58,113	$104,486	$159,745
Number of patients per centre (base case: 8 in Years 1-3, 10 in Years 4-5)					
6 per centre in Years 1-5	N=18 $17,494	N=30 $29,989	N=42 $43,388	N=60 $64,049	N=90 $97,204
12 per centre in Years 1-5	N=36 $34,200	N=60 $59,977	N=84 $87,564	N=120 $128,097	N=180 $194,408
Number of centres (base case: 3, 5, 7, 10, 15 in Years 1-5)					
4, 6, 8, 11, 16 centres in Years 1-5	N=32 $30,225	N=48 $48,538	N=64 $67,270	N=110 $115,839	N=160 $171,852
5, 8, 10, 15, 20 centres in Years 1-5	N=40 $38,175	N=64 $64,254	N=80 $84,192	N=150 $157,030	N=200 $216,059
Number of centres and number of patients per centre (base case: 8 patients in Years 1-3, 10 in Years 4-5; 3, 5, 7, 10, 15 centres)					
4, 6, 8, 11, 16 centres and 12 patients per centre in Years 1-5	N=48 $46,125	N=72 $72,019	N=96 $100,511	N=132 $141,949	N=192 $209,165
Substitution of UPPP (base case: 30%)					
15%	$25,426	$44,711	$65,203	$116,302	$177,075
50%	$19,124	$33,683	$49,448	$88,731	$136,112

Source: Table 51, p104 of the commentary
Abbreviations: MBS=medicare benefit schedule; UPPP=uvulopalatopharyngoplasty

In the pre-MSAC response, the applicant provided further clarification for the estimated utilisation, indicating it was based on the applicant's sales data from similar health care systems. The applicant also re-iterated that there will be natural, physical constraints (i.e. limited availability of specialists and hospitals providing the service) on the utilisation of the Inspire System which will impact on actual uptake.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
MBS item descriptor	ESC considered that: • CPAP failure and lack of tolerance to CPAP should be defined • "once per patient per lifetime" 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.
Place in clinical management	ESC noted that it was unclear whether closed loop UAS would replace other treatment options or be an additional option.
Unclear population	ESC noted the uncertainty in the applicability of the evidentiary trial (patients who had difficulty accepting or adhering to CPAP) to the MBS item descriptor (patients who have failed or are intolerant to CPAP).
Use of DISE as a prior test	ESC noted that DISE is not a well-described test, and current funding for, and utilisation of, DISE are uncertain.
Lack of comparative study results	ESC noted the potential bias associated with the subjective measures of ESS and FOSQ, but not the objective measures of AHI and ODI. This has implications for the use of ESS in the economic model.
Superior effectiveness claim not supported	ESC considered that the evidence did not support the claim of superior effectiveness.
Inferior safety	ESC considered that the claim of inferior safety, although not based on comparative evidence, was a reasonable assumption. ESC also noted the serious device-related adverse events in 6% of patients.
Overly simplistic economic model	ESC noted issues with the model structure, time horizon and estimate of effect size. ESC advised that the model should be revised to address these issues and also include objective inputs.
Policy issues	ESC noted the issues associated with likely OOP, MDT and capacity issues

ESC Discussion

ESC noted the purpose of the application requesting MBS listing of closed loop UAS) for patients who have failed or are intolerant to CPAP, for the treatment of moderate to severe OSA. ESC noted that there are likely to be other applications to MSAC for OSA treatment in the future, and it would be beneficial to develop a consistent framework for evaluating these applications.

ESC noted the proposed MBS item descriptors, and considered that the wording describing the patient characteristics should be deleted from the item descriptors for surgical repositioning or removal, and surgical replacement, as this description is not necessary (see ESC proposed changes in Table 3 and Table 4). ESC considered that CPAP failure and lack of tolerance to CPAP should be defined; and also noted that DISE is not listed on the MBS, but this is a required prior test for closed loop UAS. ESC considered that "once per patient per lifetime" was appropriate for surgical repositioning or removal of the device, but not for replacement of the device, as the entire device must be replaced at the end of the battery life (approximately 10 years). ESC also queried whether any co-claiming restrictions would be appropriate.

ESC noted the consultation feedback received and the perceived benefits for patients. ESC noted that multidisciplinary care and specialist training may have equity issues for patients in rural and remote areas.

ESC noted the clinical management algorithms and the issues raised in the commentary; in particular, that it was not clear whether closed loop UAS would replace other treatment options or be an additional option. ESC also considered that patients who are unwilling to undergo upper airway surgery may be a different population to those who are unsuitable for surgery. ESC also considered that it was unlikely that patients would be managed by a multidisciplinary team (as suggested by PASC) and queried potential issues with workforce and facility capacity.

ESC noted that the claim of inferior safety of closed loop UAS was not based on comparative studies against medical management, but considered this to be a reasonable assumption.

ESC noted the concerns raised in the commentary regarding evidence of comparative clinical effectiveness. These included that the risk of bias checklist used in the applicant developed assessment report (ADAR) was incorrectly applied, and the main study had a high risk of bias (not low as presented in the ADAR). The ADAR also did not present comparative results from the STAR study, and the claim that baseline values were representative of patients treated with medical management was not supported with evidence. ESC noted that some outcomes were objective (AHI, ODI), while others were self-reported (ESS, FOSQ). Limited evidence was provided to demonstrate that observed improvements in AHI, ODI, FOSQ and ESS outcomes represented a clinical benefit. ESC noted that the STAR study did not assess mortality or cardiac event outcomes. ESC also noted that, at the 5-year time point, only 56% of study participants (n = 71) completed a PSG sleep study. Although the withdrawal subgroup showed a change in response when therapy was withdrawn, ESC did not consider that this demonstrated that closed loop UAS was superior to medical management.

ESC agreed with the commentary that the economic model presented in the ADAR was overly simplistic. The model used treatment states rather than health states, and ESS was the only study outcome used in the model. ESC considered that the alternative models (Pietzch et al. 2015 and health technology assessment [HTA] for CPAP by McDaid 2009) had relevant health states that could be included in a revised model. ESC noted the pre-ESC response which considered that given STAR did not report cardiac event outcomes that including these in the model (like published models) would have resulted in multiple assumptions increasing the uncertainty considerably. ESC acknowledged that the lack of data is an issue and agreed with the applicant that it might be conservative to exclude cardiac event outcomes, but considered that the model structure should be driven by the assessment question, rather than data availability. The ADAR model used a 45-year time horizon. ESC noted that the device battery needs to be changed every approximately 10 years, so some patients in the model received this up to four times. However, ESC noted that the technology is likely to change over time, and therefore did not consider a time horizon of 45 years to be appropriate. ESC agreed with the commentary that a time horizon of 15-20 years would be more appropriate.

ESC noted that the benefits in the model were driven by the change in mortality with treatment. ESC considered that the effect size may be overestimated because the model applied a hazard ratio (HR) of 3.0 for mortality due to severe disease before treatment to the entire cohort, but the median AHI in the study used (Young 2008) was 29, indicating that at least half the cohort would be in the mild or moderate category instead (HR 1.6 and 1.4, respectively). ESC also noted that the Markov traces did not fit well to the Kaplan–Meier curves from Young 2008 (see Figure 4 below). ESC discussed the commentary's criticism of the use of ESS to drive utility values; ESC noted that, although the estimate of effect was much larger than that in McDaid 2009, it was consistent with the improvements seen in follow-up data up to 5 years. However, ESC noted that the ESS is self-reported and is subject to variability. Overall, ESC considered that a revised model should be developed that

addresses these issues, model structure that better aligns with published HTA application by McDaid and uses objective inputs (rather than ESS only).
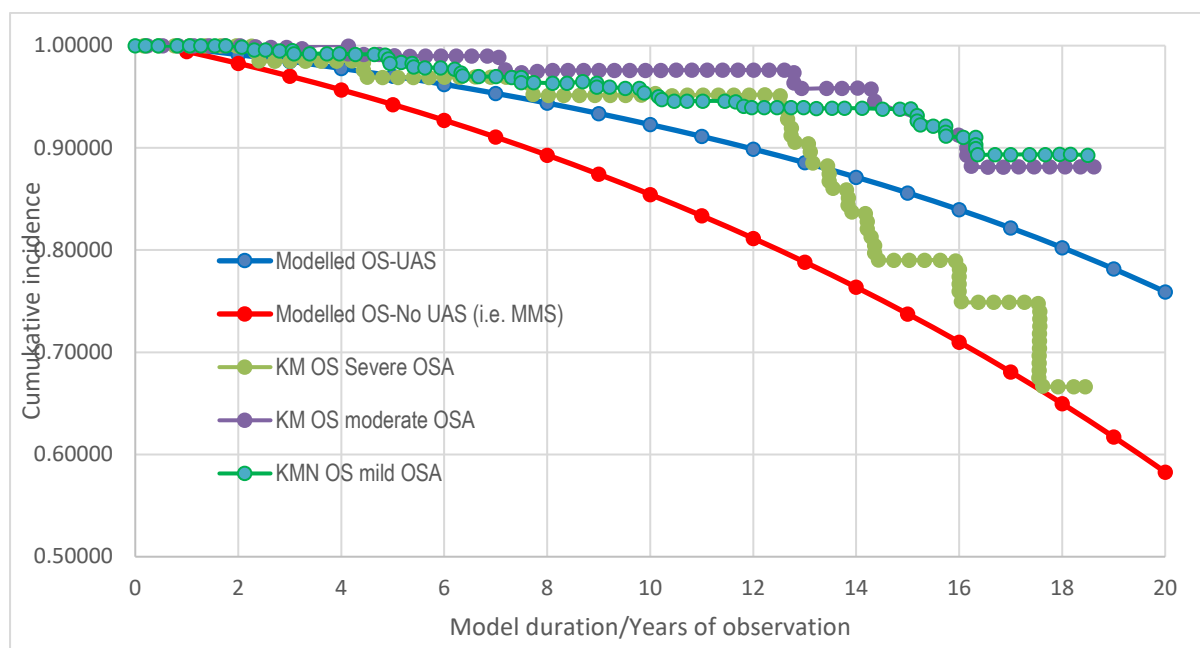

Figure 4 Comparison of ADARs modelled OS vs. digitised KM curves for mild (5 ≤ 15), moderate (15-30), severe OSA (≥30) over 20 years from Young 2008
Source: ESC meeting October 2020, created by comparing modelled OS Markov traces with digitised OSA Kaplan Meier curves from Young et al 2008 (Figure 1, p1,075)

Overall, ESC considered that the incremental cost-effectiveness ratios (ICERs) presented in the ADAR were highly uncertain due to the structural and other issues in the economic model.

ESC noted that the eligible population is potentially large, but utilisation is likely to be limited by the capacity of treatment centres and specialists. However, ESC also noted data from the United States indicating a doubling of treatment rate in the past year. ESC considered that uptake may initially be slow, but will likely increase over time when centres are operating efficiently. ESC also noted that despite the small patient numbers treated with closed loop UAS, at the applicant's proposed cost for the prostheses ($**redacted**) the potential cost to the Prostheses List would be high (e.g. $**redacted** in Year 5).

15.   Other significant factors

Nil.

16.   Applicant comments on MSAC's Public Summary Document

While disappointed with the outcome of this application, we would like to thank MSAC for their consideration of the application and the work of all those involved. It is the applicant's intention to resubmit at a later date, taking into account MSACs advice included in this document.

17.   Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website