NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

Obstructive sleep apnoea causes breathing to repeatedly stop for short periods during sleep. It happens because the muscles and soft tissues in the throat relax too much during sleep. The tongue may fall backwards and contribute to the narrowing of the upper airway. In this procedure a device is implanted under the skin in the chest. It is connected by a lead to a nerve under the tongue (hypoglossal nerve), which controls muscles in the tongue and airway. The aim is to keep the airway open during sleep.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in January 2017.

Procedure name

- Hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

Specialist societies

- British Association of Otorhinolaryngology- Head and Neck Surgery (ENT UK)
- British Association of Oral and Maxillofacial surgery
- Society of British Neurological Surgeons

- British Thoracic Society of England
- Royal College of Surgeons.

Description

Indications and current treatment

Obstructive sleep apnoea (OSA) is characterised by repeated episodes of apnoea and hypopnoea during sleep, loud snoring and excessive daytime sleepiness. The main cause is collapse of the upper airway during sleep. OSA has a big impact on quality of life and increases the risk of having a stroke and developing conditions such as hypertension and atrial fibrillation.

OSA may be improved by lifestyle changes such as weight loss, avoiding alcohol or sedative medication, and change of sleeping position. The most common treatment for severe OSA is continuous positive airway pressure, applied through a face mask during sleep. Surgical interventions include tonsillectomy, adenoidectomy, uvulopalatopharyngoplasty and, rarely, tracheostomy and bariatric surgery.

What the procedure involves

Hypoglossal nerve stimulation aims to treat obstructive sleep apnoea by preventing the tongue prolapsing backwards and causing upper airway obstruction during sleep. It works by delivering an electrical current to the hypoglossal nerve. This contracts the genioglossus muscle, the major muscle responsible for tongue protrusion, and all other intrinsic muscles of the tongue. Using general anaesthesia, a neurostimulator is implanted in an infraclavicular subcutaneous pocket and a stimulating lead is placed on the main trunk of the hypoglossal nerve. The neurostimulator delivers electrical pulses to the hypoglossal nerve. With some devices, stimulation can be synchronised with respiration using sensing leads that measure changes in breathing. The respiratory-sensing leads are positioned between the external and internal intercostal muscle. The stimulator is programmed and controlled wirelessly to adapt to specific patient needs.

Various devices can be used for this procedure.

Outcome measures

Apnoea-hypopnoea index (AHI)

AHI is an index used to indicate the severity of sleep apnoea. It is represented by the number of apnoea and hypopnea events per hour of sleep. In adults, an AHI of less than 5 events per hour is considered normal. Mild OSA is defined as an

AHI between 5 and 15 events per hour, moderate OSA between 15 and 30 events per hour, and severe OSA as greater than 30 events per hour.

Oxygen desaturation index (ODI)

The ODI is the number of times per hour of sleep that the blood oxygen level drops by ≥4 percentage points from baseline.

Epworth Sleepiness Scale (ESS)

The ESS is a validated subjective measure of sleep propensity. The ESS differentiates between average sleepiness and excessive daytime sleepiness and focuses solely on sleepiness and no other signs and symptoms of OSA. The ESS asks people to rate their usual chances of dozing off or falling asleep in 8 different situations or activities that most people engage in as part of their daily lives, although not necessarily every day. The scores range from 0 to 24 with higher scores indicating more daytime sleepiness. An ESS score of less than 10 is considered to be the threshold for normal subjective sleepiness.

Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ, a disease specific quality-of-life measure, assesses the impact of disorders of excessive sleepiness on functional outcomes relevant to daily behaviours and quality of life. The range of scores for the total score is 5–20, where a higher score implies better subjective sleep quality. A 2-point increase is considered to indicate a clinically meaningful improvement in daily functioning. Normal FOSQ score is a score greater than 17.9.

Arousal Index (AI)

The AI is the total number of arousals scored per hour of sleep. These arousals are then classified as being caused by a respiratory event, leg movement or just spontaneously.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea. The following databases were searched, covering the period from their start to 31 January 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with moderate to severe obstructive sleep apnoea.
Intervention/test	Hypoglossal nerve stimulation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 326 patients from 1 systematic review and meta-analysis[1], 4 prospective case series[2, 3, 5-7], 1 randomised controlled therapy withdrawal study[2,4] and 1 retrospective case series[8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

Study 1 Certal V F (2014)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Search date: September 2014
Study population and number	n=**200 (6 studies [5 prospective case series and 1 case report])** patients with obstructive sleep apnoea
Age and sex	Mean 54 years
Patient selection criteria	Only studies with primary objective of evaluating the efficacy of hypoglossal nerve stimulation for obstructive sleep apnoea in adults were selected. Studies were included if they provided quantitative outcomes before and after implantation of a hypoglossal nerve device for at least, the AHI, the ODI and the ESS. All studies that did not include these outcomes, polysomnogram data, or those focusing on paediatric populations were excluded.
Technique	Hypoglossal nerve stimulation using the HGNS system (Apnex Medical), the Aura6000 system (Imthera Medical) or the Inspire II upper airway stimulation device (Inspire medical systems).
Follow-up	**Range 6 to 12 months**
Conflict of interest/source of funding	None.

Analysis

Study design issues:

- Data were extracted by 2 independent reviewers in a blinded manner and discrepancies were solve by a 3rd reviewer.
- The methodological quality of the case series included was assessed by using a quality appraisal tool from NICE.
- The meta-analysis was done using the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.
- When pooling study-level data, studies with fewer than 2 patients were excluded from the calculations.
- There was no randomised trial identified in the literature search. The 5 prospective case series included were of generally high quality and satisfied the majority of the 8 items on the NICE quality-assessment tool for case series. The main methodological limitation was related to the lack of explicit statement that patients were recruited consecutively.
- The results of the studies included in the systematic review are from a few highly experienced centres.
- Hypoglossal nerve stimulation must be titrated to achieve optimal degrees of pharyngeal opening during sleep, and none of the included studies truly addressed this issue.

Study population issues: The inclusion and exclusion criteria for the studies included in the systematic review were generally highly specific. Therefore the patients included in the studies may not be representative of the population with moderate to severe OSA.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 200

AHI (mean difference from baseline)
• At 3 months, MD = -23.94 (95% CI -31.45 to -16.43), p<0.001 (34 patients)
• At 6 months, MD = -25.60 (95% CI -31.18 to -20.01), p<0.001 (60 patients)
• At 12 months, MD = -17.51 (95% CI -20.69 to -14.34), p<0.001 (170 patients)
No significant heterogeneity was found in any of the comparisons despite the use of different devices.
The overall reduction in AHI was 54% at 3 months, 57% at 6 months and 50% at 12 months.

ODI (mean difference from baseline)
• At 3 months, MD = -10.04 (95% CI -16.31 to -3.78), p<0.01 (34 patients)
• At 6 months, MD = -11.68 (95% CI -17.16 to -6.19), p<0.001 (60 patients)
• At 12 months, MD = -13.73 (95% CI -16.87 to -10.58), p<0.001 (170 patients)
No significant heterogeneity was found in any of the comparisons.
The overall reduction in ODI was 52% at 3 months, 52% at 6 months and 48% at 12 months.

ESS (mean difference from baseline)
• At 3 months, MD = -4.17 (95% CI -6.45 to -1.90), p<0.001 (34 patients)
• At 6 months, MD = -3.82 (95% CI -5.37 to -2.27), p<0.001 (60 patients)
• At 12 months, MD = -4.42 (95% CI -5.39 to -3.44), p<0.001 (170 patients)
No significant heterogeneity was found in any of the comparisons.

FOSQ
All the 4 studies including data on the FOSQ showed significant improvement, which was independent of the follow-up length.

Therapy use
3 studies reported data on therapy use that showed use on more than 85% of nights (range 86% to 96%) during 5.4 to 7.5 hours per night.

2 studies reported significant improvements in sleep apnoea quality of life index, Pittsburgh sleep quality index and Beck depression index, and 1 study reported significant improvement in the fatigue severity scale.
</td><td>
No death was reported.

Complications reported in studies included in meta-analysis
<table>
<tr><th>Complication</th><th>Study</th><th>Rate</th></tr>
<tr><td>Temporary tongue weakness</td><td>Strollo (2014)</td><td>18% (n=126)</td></tr>
<tr><td>Tongue soreness</td><td>Strollo (2014)</td><td>21% (n=126)</td></tr>
<tr><td>Transient ipsilateral hemitongue paresis</td><td>Mwenge (2013)</td><td>2/13</td></tr>
<tr><td>Pain and swelling at the neck incision site immediately postimplantation</td><td>Van de Heyning (2012)</td><td>1/22 (resolved after antibiotic treatment)</td></tr>
<tr><td>Swelling lasting for 2 weeks</td><td>Mwenge (2013)</td><td>1/13</td></tr>
<tr><td>Infection</td><td>Van de Heyning (2012)</td><td>1/22 (delayed device-related infection leading to device explantation)</td></tr>
<tr><td>Discomfort associated with stimulation</td><td>Strollo (2014)</td><td>40% (n=126)</td></tr>
<tr><td>Psychological disturbance</td><td>Kezirian (2014)</td><td>1/31 (the patient was readmitted to hospital for psychological disturbance because of a combination of self-discontinuation of antidepressant medications and prescription of opioids for pain control after the procedure)</td></tr>
<tr><td>Device-related complications requiring repositioning and fixation</td><td>Strollo (2014)</td><td>2/126</td></tr>
<tr><td>Cuff dislodgement</td><td>Eastwood (2011)</td><td>1/21 (The patient needed a new procedure to replace it)</td></tr>
<tr><td></td><td>Kezirian (2014)</td><td>2/31 (The patients needed replacement surgery)</td></tr>
<tr><td>Leads break</td><td>Mwenge (2013)</td><td>2/13</td></tr>
<tr><td>Device explantation</td><td>Eastwood (2011)</td><td>2/21</td></tr>
<tr><td></td><td>Kezirian (2014)</td><td>4/31</td></tr>
<tr><td>Defective implanted pulse generator connector</td><td>Mwenge (2013)</td><td>1/13 (The patient had the surgery but could not be implanted).</td></tr>
</table>
Other adverse events reported included: postoperative pain and stiffness, sore throat, stitch abscess, local swelling, fever, and lack of tongue response to stimulation (Van de Heyning (2012)); minor tongue abrasion (Eastwood 2010).
</td></tr>
<tr><td colspan="2">Abbreviations used: AHI, apnoea-hypopnoea index; CI, confidence interval; ESS, Epworth sleepiness scale; FOSQ, functional outcomes of sleep questionnaire; MD, mean difference; ODI, oxygen desaturation index.</td></tr>
</table>

Study 2 Strollo P J (2014) – STAR trial

Details

Study type	**Prospective case series followed by a randomised controlled therapy withdrawal trial**
Country	US and Europe (22 centres)
Recruitment period	2010-13
Study population and number	n=**126** patients with moderate to severe obstructive sleep apnoea (**case series**) **Randomised phase** n= **46** (23 therapy-maintenance versus 23 therapy-withdrawal) consecutive patients with a response to therapy
Age and sex	Mean 55 years; 83% (105/126) male Mean body mass index (BMI): 28.4 kg/m^2
Patient selection criteria	**1/ Case series** Inclusion criteria: Patients with moderate to severe obstructive sleep apnoea with difficulty accepting or adhering to continuous positive airway pressure (CPAP) treatment. Exclusion criteria: BMI of more than 32, neuromuscular disease, hypoglossal nerve palsy, severe restrictive or obstructive pulmonary disease, moderate-to-severe pulmonary arterial hypertension, severe valvular heart disease, New York Heart Association class III or IV heart failure, recent myocardial infarction or severe cardiac arrhythmias (within the past 6 months), persistent uncontrolled hypertension despite medication use, active psychiatric disease, and coexisting non-respiratory sleep disorders that would confound functional sleep assessment. AHI score of less than 20 or more than 50 events per hour, central or mixed sleep disordered breathing events accounting for more than 25% of all apnoea and hypopnea episodes, or AHI score while the person was not in a supine position of less than 10 events per hour. Pronounced anatomical abnormalities preventing the effective use or assessment of upper-airway stimulation or complete concentric collapse at the retropalatal airway. **2/ RCT** Subgroup of consecutive patients selected from the population that had a response to therapy (defined as the patients who completed the 12-month visit).
Technique	Hypoglossal nerve stimulation using the Inspire Medical Systems device. The device was activated 1 month after implantation. Patients were instructed regarding the use of a controller to initiate and terminate therapy on a nightly basis.
Follow-up	**1 year**
Conflict of interest/source of funding	The STAR study was funded by Inspire medical Systems.

Analysis
Follow-up issues:
- After activation, patients had scheduled outpatient visits at months 2, 3, 6, 9, and 12; at each of these visits data on adverse events were obtained and device interrogation was performed.
- After the 12-month visit, the patients randomly assigned to the therapy-withdrawal group had the device turned off for 7 days and the patients randomly assigned to the therapy-maintenance group continued with the device turned on.
- 98% (124/126) of patients completed the follow-up at 12 months. One patient died from a cardiac event thought to be unrelated to the device and 1 patient elected to remove the device.

Study design issues:
- An independent clinical-events committee and a data and safety monitoring board provided review and adjudication of safety data. Verification of source data was performed by independent monitors. The study investigators had full access to the data and had the right to submit the manuscript for publication without input from the sponsor.
- The primary outcome measures were the AHI and the ODI.
- Baseline measurements were the averages of the measurements obtained before implantation and at the 1-month preactivation visit.
- It was estimated that 108 patients had to be enrolled for the study to have 80% power to evaluate the primary outcome, with the exact one-sided binomial test set at a significance level of 2.5%.
- In the randomised controlled therapy withdrawal trial, it was estimated that 40 participants would need to undergo randomisation in a 1:1 ratio in order for the study to have 80% power to detect a significant difference between groups, at the 5% significance level, with the use of a two-sided t-test.

Study population issues:
- All patients had a history of nonadherence to CPAP therapy; 17% had had an uvulopalatopharyngoplasty.

Other issues: This study was included in the Certal (2014) systematic review and meta-analysis.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **126**

Procedure outcomes

- The device was successfully implanted in all 126 patients.
- The median time for surgical implantation was 140 minutes (range, 65 to 360).
- Patients were discharged after surgery on the same day (16% of patients), the next day (79%), or the second day after surgery (5%).

Outcome measures (means±SD)

	Baseline	1 year	Change	p value
AHI score (events per hour)	32.0±11.8	15.3±16.1	−16.4±16.7	<0.001
Median	29.3	9.0	−17.3	
Interquartile range	23.7 to 38.6	4.2 to 22.5	−26.4 to −9.3	
ODI score	28.9±12.0	13.9±15.7	−14.6±15.8	<0.001
Median	25.4	7.4	-15.7	
Interquartile range	19.5 to 36.6	3.5 to 20.5	−24.0 to −8.6	
FOSQ score	14.3±3.2	17.3±2.9	2.9±3.1	<0.001
Median	14.6	18.2	2.4	
Interquartile range	12.1 to 17.1	16.2 to 19.5	0.7 to 4.7	
ESS score	11.6±5.0	7.0±4.2	−4.7±5.0	<0.001
Median	11.0	6.0	-4.0	
Interquartile range	8.0 to 15.0	4.0 to 10.0	−8.0 to −1.0	
% of sleep time with oxygen saturation <90%	8.7±10.2	5.9±12.4	−2.5±11.1	0.01
Median	5.4	0.9	−2.2	
Interquartile range	2.1 to 10.9	0.2 to 5.2	−6.6 to −0.3	

Therapy-withdrawal study

	Baseline	At 1 year - randomised phase	At 1 week after randomisation
AHI score (events per hour)			
Therapy-maintenance group (n=23)	31.3	7.2	8.9
Therapy-withdrawal group (n=23)	30.1	7.6	25.8
ODI (mean scores)			
Therapy-maintenance group (n=23)	26.7	6.3	8.0
Therapy-withdrawal group (n=23)	26.8	6.0	23.0

- Statistically significant difference between AHI and ODI scores at 1 week post-randomisation and scores at 1 year in the therapy-withdrawal group (p<0.001).
- Statistically significant difference in changes between groups in mean AHI and ODI scores from 1-year assessment to the assessment 1 week after randomisation (p<0.001).

Safety

Summary of adverse events (follow-up = mean 628 days)

Adverse events	Number of events	Number of patients with event
Serious adverse events	35	21% (27/126)
Device-revision	2	2% (2/126)
Death, unrelated[a]	2	2% (2/126)
Other unrelated*	31	18% (23/126)
Procedure-related non-serious adverse event	169	57% (72/126)
Post-op discomfort related to incisions	46	26% (33/126)
Post-op discomfort not-related to incision	39	25% (31/126)
Temporary tongue weakness	35	18% (23/126)
Intubation effects	18	12% (15/126)
Headache	8	6% (8/126)
Other post-op symptoms	22	11% (14/126)
Mild infection	1	1% (1/126)
Device-related non-serious adverse event	190	67% (85/126)
Discomfort due to electrical stimulation	80	40% (50/126)
Tongue abrasion	33	21% (26/126)
Dry mouth	13	10% (13/126)
Mechanical pain associated with device presence	8	6% (8/126)
Temporary internal device functionality complaint	14	10% (12/126)
Temporary external device usability or functionality complaint	8	6% (7/126)
Other acute symptoms	25	15% (19/126)
Mild or moderate infection**	1	1% (1/126)

* Other unrelated serious adverse events included cardiac conditions: coronary artery disease, arrhythmias, and chest pain (n = 8), accidents or injuries (n = 11), and other surgeries (n=12).
**Skin cellulitis.
[a] One death from a cardiac event thought to be unrelated to the device, one death related to a homicide.

Elective device removal (1/126)

- Most of non-serious adverse events related to the procedure (88%) occurred within 30 days after implantation.
- Most of the device-related adverse events resolved after the patients acclimated to the upper-airway stimulation therapy or after the device was reprogrammed to adjust the stimulation variables. In 9 patients, a tooth guard was used to resolve tongue soreness or abrasion related to the device.

Abbreviations used: AHI, apnoea-hypopnoea index; ESS, Epworth sleepiness scale; FOSQ, functional outcomes of sleep questionnaire; NS, not statistically significant; ODI, oxygen desaturation index; SD, standard deviation.

Study 3 Woodson B T (2016) – 3-year follow-up from STAR trial

Details

Study type	**Prospective case series**
Country	US and Europe (22 centres)
Recruitment period	2010-13
Study population and number	n= **116** patients with moderate to severe obstructive sleep apnoea at 3 years from a cohort of 126 patients
Age and sex	Mean 54 years; gender not reported Mean body mass index (BMI): 28.6 kg/m^2
Patient selection criteria	Inclusion criteria: adults with a history of moderate to severe OSA and intolerance or inadequate adherence to CPAP. Exclusion criteria: BMI>32 kg/m^2, neuromuscular disease (including hypoglossal nerve palsy or injury), severe cardiopulmonary disorders, active psychiatric disease, and comorbid non-respiratory sleep disorders that would confound functional sleep-related assessments. AHI <20 or >50 events/hour sleep, central and/or mixed apnoea index >25% of the AHI, or a nonsupine AHI<10. Pronounced anatomic abnormalities preventing effective use of the device. Patients with observed complete concentric collapse at the level of the velopharynx.
Technique	Hypoglossal nerve stimulation using the Inspire Medical Systems device. The device was activated 1 month after implantation. During the first month of at-home use, patients gradually increased the stimulation amplitude to facilitate therapy acclimatisation and to optimise both comfort and subjective effectiveness. Between 2 and 6 months, ≥1 in-laboratory polysomnography titration studies were conducted to optimise therapy. Additional titration studies were performed in some patients after 6 months based on previous titration results and patient feedback.
Follow-up	**3 years**
Conflict of interest/source of funding	The STAR study was funded by Inspire medical Systems.

Analysis
Follow-up issues:
- 92% (116/126) of patients completed the 36-month follow-up evaluation per protocol; 98 patients additionally agreed to a voluntary 36-month polysomnography.
- All participant self-reported outcomes were followed at 6-month intervals for 3 years. Polysomnography data were collected at 12- and 18-month follow-up visits per the protocol.
- 3% (4/126) of patients were lost to follow-up.

Study design issues: Prospective outcomes included apnoea hypopnea index, oxygen desaturation index, other polysomnography measures, self-reported measures of sleepiness, sleep-related quality of life, and snoring.
Study population issues: The group of 98 patients who agreed to complete the interim polysomnography study did not significantly differ in baseline characteristics from the original or 12-month data groups. However, it differed in having a lower percentage of 12-month non-responders than the group that did not volunteer.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **116**

Outcome measures for patients with completed polysomnography at 3 years (n=98)

				Change (95% CI; p value)		
	Baseline	**1 year**	**3 years**	**Baseline to 1 year**	**Baseline to 3 years**	**1 year to 3 years**
AHI score (events per hour)	30.4±10.4	13.5±14.3	11.5±13.9	16.9 (13.9 to 19.9; p<0.001)	18.8 (16.1 to 21.6; p<0.001)	1.95 (-1.0 to 4.9; p=0.20)
Median	28.2	8.7	6.2	17.4	19.4	0.6
ODI score (events per hour)	27.1±10.8	12.0±13.6	9.1±11.7	15.1 (12.3 to 17.9; p<0.001)	18.0 (15.5 to 20.4; p<0.001)	2.86 (0.4 to 5.3; p=0.02)
Median	24.3	7.1	4.8	15.5	17.2	1.1
SaO_2 <90%	7.9±9.7	5.0±11.2	5.7±10.2	2.9 (1.0 to 4.8; p=0.01)	2.2 (-0.1 to 4.5; p=0.06)	-0.73 (-2.7 to 1.2; 0.46)
Median	4.8	0.7	1.0	2.1	1.5	0.0

Results in mean ± SD.

Treatment success at 3 years (AHI decrease of >50% to <20)
74% (73/98)

Self-reported quality-of-life outcome for patients who completed follow-up at 36 months (n = 113)

				Change (95% CI; p value)		
	Baseline	**1 year**	**3 years**	**Baseline to 1 year**	**Baseline to 3 years**	**1 year to 3 years**
FOSQ	14.6±3.0	17.6±2.4	17.4±3.5	-3.0 (-3.5 to -2.5; p<0.001)	-2.7 (-3.4 to -1.9; p<0.001)	0.4 (-0.2 to 1.0; p=0.20)
Median	15.1	18.3	18.8	-2.5	-2.6	0.0
ESS	11.4±5.1	6.9±4.3	7.0±5.0	4.5 (3.6 to 5.5; p<0.001)	4.5 (3.3 to 5.4; p<0.001)	-0.04 (-0.7 to 0.6; p=0.92)
Median	11	6	6	4	4	0

Snoring (% of bed partner–reported no snoring or soft snoring)
17% (18/108) at baseline; 86% (89/103) at 1 year; 80% (78/97) at 3 years

Therapy use (subjective report of nightly therapy use)

- 86% (100/116) at 12 months; 81% (94/116) at 24 and 36 months.
- 21 patients at 3 years reported not using therapy every night. Of these, 10 reported therapy use for at least 4 nights each week. The other 11 patients, who reported <4 nights per week of use, described this as the result of discomfort related to stimulation (n =

Safety

Death due to unrelated causes: 3/126

Serious adverse events (1- to 3- year follow-up)

Elective device removal (2/126)
1 was due to insomnia and 1 was due to device-unrelated septic arthritis.

Non-serious adverse events (mean 40-month follow-up)

Adverse events	Nb of events 0-12 M	Nb of events 12-14 M	Nb of events post 24M	Nb of events total	Nb of patient with event (n=126)
Procedure-related non-serious adverse events					
Post-operative discomfort related to incisions	47	1	2	50	29% (37/126)
Post-operative discomfort independent of incisions	41	0	1	42	27% (34/126)
Temporary tongue weakness	34	0	0	34	18% (23/126)
Intubation effects	18	0	0	18	12% (15/126)
Headache	8	0	0	8	6% (8/126)
Other post-op symptoms	22	0	0	22	11% (14/126)
Mild infection	1	0	0	1	1% (1/126)
Device-related non-serious adverse event					
Discomfort due to electrical stimulation	80	23	24	127	56% (70/126)
Tongue abrasion	28	13	4	45	25% (32/126)
Dry mouth	11	5	1	17	13% (16/126)
Mechanical pain associated with presence of the device	7	2	4	13	10% (12/126)
Temporary internal device usability or functionality complaint	12	7	1	20	13% (17/126)
Temporary external device usability or	**11**	**11**	**11**	**33**	**19% (24/126)**

5), forgetting to turn device on (n = 2), other sleep disorders (n = 2), and 1 each because of lost remote or a return to CPAP.	**functionality complaint** | | | | | | **Other acute symptoms** | **22** | **15** | **1** | **38** | **22% (28/126)** **Mild infection** | **1** | **0** | **0** | **1** | **1% (1/126)**
Abbreviations used: AHI, apnoea-hypopnoea index; CI, confidence interval; CPAP, continuous positive airway pressure; ESS, Epworth sleepiness scale; FOSQ, functional outcomes of sleep questionnaire; M, month; Nb, number; NS, not statistically significant; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; SD, standard deviation.	

Study 4 Woodson B T (2014) - Cohort of 46 responders from STAR trial

Details

Study type	**Randomised controlled therapy withdrawal study**
Country	US and Europe (22 centres)
Recruitment period	2010-13
Study population and number	n= **46 (23 therapy-ON versus 23 therapy-OFF)** consecutive patients with a response to therapy from the STAR trial
Age and sex	ON group: Mean 57 years; 96% (22/23) male OFF group: Mean 53 years; 83% (19/23) male
Patient selection criteria	Subgroup of consecutive patients selected from the population of the STAR trial that had a response to therapy
Technique	ON group: Hypoglossal nerve stimulation using the Inspire Medical Systems device. Patients continued nightly use of the device and therapy remained on until and during the RCT polysomnography. OFF group: The device was turned off for a minimum of 1 week and remained off until the RCT polysomnography was performed. It was then turned on again.
Follow-up	**18 months after implantation**
Conflict of interest/source of funding	The STAR study was funded by Inspire medical Systems.

Analysis

Follow-up issues: Of the 46 participants randomised, no one was lost to follow-up at the RCT and 1 patient in the therapy ON group was lost to 18-month follow-up.

Study design issues:

- Changes in AHI and ODI between the 12-month RCT polysomnography and 18-month polysomnographies were the primary measures.
- The study was not blinded.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **46 (23 therapy-ON versus 23 therapy-OFF)**

Polysomnographic outcomes at baseline, 12-month, RCT and 18-month follow-up.

	''ON'' Group	''OFF'' Group	Difference (ON – OFF, 95% confidence level)	p value
AHI				
Baseline	31.3±12.3	30.1±11.4	1.2 (-5.8 to 8.3)	0.73
12 month	7.2±5.0*	7.6±4.0*	-0.4 (-3.1 to 2.3)	0.74
RCT	8.9±9.1*	25.8±16.2	-16.9 (-24.7 to -9)	<0.001
18 month	9.6±11.3*	10.7±7.3*	-1.1 (-6.9 to 4.7)	0.85
ODI				
Baseline	26.7±13.0	26.8±10.2	-0.1 (-7.0 to 6.9)	0.98
12 month	6.3±5.4*	6.0±3.7*	0.3 (-2.4 to 3.1)	0.81
RCT	8.0±8.9*	23.0±15.6	-15.1 (-22.7 to -7.5)	<0.001
18 month	8.6±11.0*	9.1±6.1*	-0.5 (-5.9 to 5.0)	0.86
% sleep SaO_2 <90%				
Baseline	7.4±8.3	5.6±4.4	1.8 (-2.1 to 5.8)	0.35
12 month	3.2±8.3	1.0±2.0*	2.1 (-1.6 to 5.7)	0.23
RCT	4.2±6.2*	7.5±10.5	-3.3 (-8.4 to 1.9)	0.20
18 month	7.6±17.8	1.7±6.2*	5.8 (-2.1 to 13.8)	0.12
Arousal index				
Baseline	30.9±13.5	26.2±14.6	4.7 (-3.6 to 13.1)	0.26
12 month	12.0±5.0*	13.9±8.0*	-1.4 (-4.8 to 2.1)	0.35
RCT	13.2±9.9*	30.9±16.4	-17.7 (-25.8 to -9.6)	<0.001
18 month	14.8±10.4*	17.2±9.9*	-2.4 (-8.4 to 3.7)	0.43

***p < 0.05 versus baseline within the group**

No changes in N1, N2, N3, REM sleep, sleep efficiency, or other sleep-related variables were observed with therapy withdrawal or therapy resumption.

Self-reported quality of life outcomes

	''ON'' Group	''OFF'' Group	Difference (ON – OFF, 95% confidence level)	p value
Functional Outcomes of Sleep Questionnaire				
Baseline	15.1±3.1	13.9±2.6	1.3 (-0.4 to 3.0)	0.15
12 month	17.9±2.9*	17.0±3.5*	0.9 (-1.0 to 2.8)	0.36
RCT	17.9±2.9*	15.0±4.0	2.9 (0.8 to 5.0)	0.008
18 month	18.0±2.9*	17.1±2.9*	0.9 (-0.8 to 2.6)	0.29
Epworth Sleepiness Scale				
Baseline	11.2±5.3	11.3±5.0	0.4 (-2.8 to 3.6)	0.97
12 month	5.9±3.4*	6.9±4.6*	-1.0 (-3.4 to 1.5)	0.43
RCT	5.6±3.9*	10.0±6.0	-4.5 (-7.5 to -1.4)	0.005
18 month	6.0±3.7*	8.0±4.4*	-2.0 (-4.5 to 0.4)	0.09

***p < 0.05 versus baseline within the group**

Snoring

- Snoring severity measured by the percentage of soft or no snoring reported by self and bed partner improved in both groups from baseline to 12 months.
- The percentage of soft or no snoring significantly decreased with therapy withdrawal and returned to treatment baseline at 18 months.

Safety

No safety outcomes reported.

Abbreviations used: AHI, apnoea-hypopnoea index; ESS, Epworth sleepiness scale; FOSQ, functional outcomes of sleep questionnaire; ODI, oxygen desaturation index; RCT, randomised controlled trial; SD, standard deviation.

Study 5 Heiser C (2017) a

Details

Study type	**Prospective case series**
Country	Germany (3 centres)
Recruitment period	2014-15
Study population and number	n= **60** patients with moderate to severe obstructive sleep apnoea
Age and sex	Mean 57 years; gender not reported
Patient selection criteria	Inclusion criteria: Patients with moderate to severe obstructive sleep apnoea and a history of non-adherence to CPAP. Selection criteria were based on those established from the STAR trial. Exclusion criteria: BMI>35 kg/m^2, AHI<15 or >65, central sleep apnoea >25% of total AHI or complete concentric collapse of the soft palate during drug-induced sedated endoscopy.
Technique	Hypoglossal nerve stimulation using the Inspire Medical Systems device. The device was activated 1 month after implantation, followed by a month of therapy acclimatisation, with patient gradually increasing the amplitude of stimulation. Between months 2 and 6, in-laboratory titration studies were conducted to optimise therapy during polysomnography.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was sponsored and funded by Inspire Medical Systems.

Analysis

Follow-up issues:

- A 2-night home sleep test was done before and after surgery.
- 93% (56/60) of patients completed the 6-month follow-up visit. The remaining 4 patients underwent a uvulopalatopharyngoplasty surgery after the 2-month titration studies and missed the 6-month visit.

Study population issues:

- All patients had failed CPAP as a first-line treatment.
- 23% (14/60) of patients had also attempted oral appliance therapy but could not maintain adherence, primarily due to insufficient efficacy.
- 25% (15/60) of patients had prior upper airway OSA operations

Other issues: There is a probable overlap between patients included in this study and patients included in the other Heiser (2017b) study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **56**

Polygraphic outcomes (averaged 2-night results)

	Baseline	6 months	p value
AHI (events/ h)			<0.001
Mean ± SD	31.2±13.2	12.0±9.8	
Median (range)	28.6 (12.3-64.5)	8.3 (0.8-34)	
ODI (events/ h)			<0.001
Mean ± SD	27.6±16.4	13.5±10.7	
Median (range)	27.0 (3.5-60.9)	9.6 (0.5-35.5)	
Apnoea index (events/ h)			<0.001
Mean ± SD	18.1±14.7	7.6±7.8	
Median (range)	14.2 (2.2-64.5)	4.9 (0-33.7)	
Hypopnea index (events/h)			<0.001
Mean ± SD	13.0±7.2	4.4±4.1	
Median (range)	12.4 (0-33.7)	3.2 (0.2-20.4)	
Central + mixed apnoea index (events/h)			0.27
Mean ± SD	1.2±2.3	0.8±1.1	
Median (range)	0.4 (0-11)	0.3 (0-4.6)	
Min SpO_2 (%)			<0.001
Mean ± SD	71.4±11.4	80.4±7.6	
Median (range)	73.8 (50.5-88)	81 (65-90.5)	
Mean SpO2 (%)			0.41
Mean ± SD	92.8±1.9	93.2±3.4	
Median (range)	93 (86.5-97)	93.5 (73-97)	
Total sleep time SpO_2<90% (min)			0.07
Mean ± SD	45.3±60.5	25.8±34.8	
Median (range)	13.4 (0-272)	8.8 (0-141)	
% of sleep time SpO_2 <90%			0.26
Mean ± SD	10.7±13.9	7.1±12.1	
Median (range)	3.2 (0-56.7)	2 (0-75.5)	

- AHI reduction at 6 months: 61% ± 24%
- At the 6-month visit, 25% of patients had an AHI ≤ 5 events/h, 59% an AHI ≤ 10/h and 70% an AHI≤15h.
- Responders (AHI<20 with at least 50% reduction): 63% (n=60)

Patient-reported outcomes at baseline and 2- and 6-month follow-up

	Baseline	2 mo	6 mo	p value Baseline vs 2 mo	p value Baseline vs 6 mo	p value 2 mo vs 6 mo
ESS				<0.001	<0.001	<0.001
Mean±SD	12.8±5.4	9.0±4.8	7.0±4.5			
Median (range)	13.5 (2-24)	8.0 (0-21)	6.0 (0-17)			
FOSQ				<0.001	<0.001	<0.002
Mean±SD	13.2±3.5	15.2±4.1	16.9±2.9			
Median (range)	13.3 (5-19.8)	15.7 (5.1-20)	17.8 (9.2-20)			

Mean therapy use at 6 months: mean 42.9±11.9 h/week (range 9 to 64 h/week)

Safety

Adverse event	Number of patients
Bleeding during tunnelling of stimulation lead from the neck incision to the device pocket	3% (2/60)
Postoperative pain related to the incision	8% (5/60)
Acute tongue numbness	2% (1/60) It resolved within 2 months.
Dysarthria	2% (1/60) It resolved within 2 months.
Painful stimulation sensation after therapy activation	5% (3/60) 2 resolved without intervention. One patient was still monitored.
Speech difficulties after therapy activation	2% (1/60) This was resolved through reprogramming the stimulation energy field parameters.

Abbreviations used: AHI, apnoea-hypopnoea index; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; ESS, Epworth sleepiness scale; FOSQ, functional outcomes of sleep questionnaire; Mo, month; Nb, number; NS, not statistically significant; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; SD, standard deviation.

Study 6 Friedman M (2016)

Details

Study type	**Prospective case series**
Country	US, Germany and Belgium (7 centres)
Recruitment period	2013
Study population and number	n= **46** patients with moderate to severe obstructive sleep apnoea
Age and sex	Mean 55 years; 93% (43/46) male Mean BMI 31 kg/m^2
Patient selection criteria	Inclusion criteria: adults with site-scored baseline AHI≥20 and BMI≤37 who did not tolerate positive airway pressure treatment. Exclusion criteria: ≥10% central sleep apnoea, clinically enlarged tonsils, Modified Mallampati IV, nasal obstruction, syndromic craniofacial abnormalities, epiglottic obstruction and evidence of positional OSA. Patients with other active implanted medical devices.
Technique	Hypoglossal nerve stimulation using the Imthera aura6000 system. Following a 3- to 4-week healing period, patients underwent in-laboratory polysomnography and titration of the device.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was funded by Imthera medical.

Analysis

Follow-up issues:

- 93% (43/46) of patients completed 6-month follow-up: 1 withdrew consent, 1 was withdrawn by the physician and 1 missed the 6-month follow-up.

Study design issues:

- Feasibility study.
- The primary safety endpoints assessed serious adverse events within 30 days and 6 months after the implantation.
- The primary efficacy endpoints assessed changes in AHI and ODI from baseline to 6 months after implantation.
- AHI responders were predefined as ≥ 50% reduction in AHI and a resulting AHI of less than 20/hour. ODI responders were predefined as having a greater than 50% reduction in ODI.
- Patients were implanted based on site-scored polysomnography rather than a centrally-scored study.

Study population issues:

- 1 patient had prior surgical treatment for OSA (uvulopalatopharyngoplasty).

Other issues: The device used targets 6 sections of the hypoglossal nerve for stimulation and does not have a respiration-sensing lead.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **43**

Primary and secondary outcomes (n=43)

Variable	Responder status	Baseline Mean±SD	6 months Mean±SD	p*
AHI	Combined	34.9±22.5	25.4±23.1	0.004
	Yes, n=15	35.7±19.4	8.5±5.9	<.0001
	No, n=28	34.5±24.3	34.5±23.8	0.9860
ODI	Combined	32.4±22.3	23.6±22.3	0.006
	Yes, n=17[a]	32.6±18.9	7.9±5.5	<.0001
	No, n=26	32.3±24.2	32.1±23.4	0.9224
ArI	Combined	42.7±19.4	31.6±20.3	<.001
	Yes, n=15	43.9±17.0	20.4±9.3	<.0001
	No, n=28	42.1±20.9	37.6±22.2	0.1711
ESS	Combined	12.0±4.8	8.3±4.4	<.001
	Yes, n=15	13.0±5.6	8.4±5.2	0.0049
	No, n=28	11.5±4.3	8.2±4.0	0.0004
SAQLI	Combined	4.3±1.0	4.7±1.2	0.019
	Yes, n=15	4.3±1.1	5.0±1.4	0.0211
	No, n=28	4.3±1.1	4.6±1.1	0.1927

*****Based on a paired t test.

[a]ODI responders.

Predictors of success

Baseline AHI<65/h, baseline apnoea index ≤30, baseline BMI<35 and less than 15 events/h where SpO_2 decrease >10%.

Safety

Adverse events (number of events [% of population, number of patients])

	Nonserious		Serious	
Adverse event	**Within 30 days of implantation**	**More than 30 days after implantation**	**Within 30 days of implantation**	**More than 30 days after implantation**
Anaesthesia complication	1 (2% [1/46])	-	-	-
Haematoma	1 (2% [1/46])	1 (2% [1/46])	1 (2% [1/46])	-
Infection	4 (9%[4/46])	-	-	-
Pain	7 (15% [7/46])	12 (20% [9/46])	1 (2% [1/46])	2 (4% [2/46])
Paresis	5 (11% [5/46])	-	-	-
Paraesthesia	5 (11% [5/46])	1 (2% [1/46])	-	-
Bleeding	-	-	1 (2% [1/46])	-
No stimulation at 29 days	-	-	1 (2% [1/46]) Resolved by lead revision.	-
Device migration	-	-	-	1 (2% [1/46])
Other	1 (2% [1/46])	16 (28% [13/46])	2 (4% [2/46])	3 (7% [3/46])
Totals	24 (37% [17/46])	31 (44% [20/46])	6 (13% [6/43])	6 (11% [5/46])
Events related to the procedure or device	92% (22/24)	61% (19/31)	83% (5/6)	50% (3/6)

- Serious adverse events were defined as resulting in death, life-threatening illness or injury, permanent impairment of body structure or function, hospitalisation (>24 hours) or prolongation of existing hospitalisation, or medical or surgical intervention to prevent permanent impairment.
- Short-term non-serious events: All were transient and resolved with minimal or no intervention. Among reports of pain, 4 involved the area around the neck incision. All 5 reports of paresis and 1 report of paresthesia resolved spontaneously.
- Long-term non-serious events: 10 reports of pain were related to the procedure or device. 6 of these described overstimulation, which was resolved by titration in 6 cases; 2 needed rebooting the device to set the stimulation parameters correctly. The remaining reports involved tenderness around the incision site that resolved within 1 month and 1 report of tongue soreness that resolved without treatment.
- Short-term serious events: 2 reports required revision or replacement; pain at 30 days was resolved by replacement of the IPG. The patient with the haematoma at the lead implant site received intravenous clindamycin. The bleeding event was caused by a hypertensive crisis and required intervention in the operative room; hypertension was treated with medication.
- Long-term serious events: One pain event was resolved by replacing the IPG. The 2 other events related to the procedure or device occurred in a single hypertensive patient who needed surgical revision 50 days after surgery because excessive subcutaneous fat was contributing to charging difficulties. The first event, involving a combination of a haematoma and an infection was revised surgically; additional treatment was needed 2 weeks later because of recurrence of the haematoma.

Abbreviations used: AHI, apnoea-hypopnoea index; ArI, arousal index; BMI, body mass index; ESS, Epworth sleepiness scale; IPG, implantable pulse generator; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; SAQLI, Sleep apnoea quality of life index; SD, standard deviation.

Study 7 Heiser C (2017) b

Details

Study type	**Prospective case series**
Country	Germany (1 centre)
Recruitment period	2014-15
Study population and number	n= **31** consecutive patients with moderate to severe OSA
Age and sex	Mean 60 years; 97% (30/31) male Mean BMI: 28.8 kg/m^2
Patient selection criteria	Inclusion criteria: AHI>15/h and <65/h, central apnoea index<25% and nonadherence to CPAP treatment. Exclusion criteria: BMI>35 kg/m2, pronounced anatomical abnormalities preventing use of the device, complete concentric collapse of the soft palate during drug-induced sedated endoscopy, chronic obstructive pulmonary disease, New York Heart Association class III or IV heart failure, neuromuscular diseases, hypoglossal nerve palsy, recent myocardial infarction or severe cardiac arrhythmias, persistent uncontrolled hypertension despite medication use, active psychiatric disease and the foreseeable need of magnet resonance imaging .
Technique	Hypoglossal nerve stimulation using the Inspire II Upper Airway Stimulation System (Inspire Medical Systems). All patients were discharged on the third day after the procedure. Postoperative examination with the removal of the stitches was done within 1-2 weeks. The device was activated 1 month after the procedure and the patients were instructed in the use of the controller to initiate and terminate the therapy for night time home use. They were told to increase the strength of the stimulation gradually from the initially programmed amplitude, and followed by a phone call 1 week later for the acclimatisation status of therapy.
Follow-up	**1 year**
Conflict of interest/source of funding	The main author of the paper is a study investigator and consultant of Inspire Medical System and received personal fees, travel expenses and research grants. The other authors have no conflict of interest.

Analysis
Follow-up issues:

- Follow-up visits were scheduled at month 1, 2, 3, 6 and 12.
- No patient was lost to follow-up and all patients completed the follow-up period of 12 months.

Study population issues: The mean time between the first diagnosis of OSA to the date of implantation was 34 months.
Other issues: There is a probable overlap between patients included in this study and patients included in the other Heiser (2017a) study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **31**

Surgical implantation success: 100% (31/31)

Outcome measures (mean±SD)

	Baseline	M2	p value	M3	p value	M6	p value	M12	p value
AHI	32.9/h±11.2	11.5/h±14.1	<0.001	10.3/h±13.0	<0.001	7.6/h±5.3	<0.001	7.1/h±5.9	<0.001
ODI	30.7/h±14.0	13.7/h±12.2	<0.001	13.8/h±13.8	<0.001	11.7/h±8.8	<0.001	9.9/h±8.0	0.004
Mean SpO2	92.3%±2.4	93.8%±2.0	<0.001	93.7%±2.0	0.001	92.9%±3.4	0.762	93.1%±1.9	0.307
Min SpO2	74.1%±11.4	83.8%±5.2	<0.001	84.5%±5.6	<0.001	79.1%±11.1	0.108	79.3%±11.6	0.151
ESS	12.6±5.6	8.6±5.0	<0.001	6.8±4.8	<0.001	5.9±4.8	0.001	5.9±5.2	0.006

p value was given for the differences compared to baseline.

Therapy adherence

	Month 2	Month 3	Month 6	Month 12
Rate of therapy adherence	7.0±1.5 h/ night	6.9±2.3 h/ night	6.0±2.2 h/ night	6.6±2.7 h/ night

Safety

Adverse events during the procedure

Rupture of venous vessel during cervical tunnelling: 6% (2/31). One of the patients needed 1 further cervical incision.

Abbreviations used: AHI, apnoea-hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth sleepiness scale; IPG, implantable pulse generator; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; SD, standard deviation.

Study 8 Kent D T (2016)

Details

Study type	**Retrospective case series**
Country	USA (single centre)
Recruitment period	2014-15
Study population and number	n= **20** patients with moderate to severe OSA
Age and sex	Mean 65 years; 50% (10/20) male Mean BMI; 26.5 kg/m^2
Patient selection criteria	Inclusion criteria: BMI ≤32 kg/m^2 and a diagnosis of moderate to severe OSA (central apnoea index <25%). All patients were unable to adhere to PAP despite multiple attempts and mask refits. Patients presenting with primarily anterior-posterior pattern of pharyngeal collapse during drug-induced sedation endoscopy (DISE) with evidence of mechanical coupling between the tongue and palate. Exclusion criteria: Patients with a primary pattern of complete concentric palatal collapse with a large lateral oropharyngeal wall component during DISE.
Technique	The Inspire HNS system (Inspire Medical Systems) was implanted. All patients received preoperative antibiotics via one intravenous dose 30 to 60 minutes before the skin incision. The surgical implantation procedure was performed as outpatient surgery.
Follow-up	**Mean 233 days (range 109-400 days)**
Conflict of interest/source of funding	Ryan J. Soose is a consultant for Inspire Medical Systems and has provided research support as an investigator in the STAR trial. Patrick Strollo is a study investigator for Inspire Medical Systems; is on the scientific advisory board and has received grant support from ResMed; is on the scientific advisory board of Jazz Pharmaceuticals; is a consultant for Emmi Solutions, PinMed, and the National Football League; and has received grant support from Philips Respironics and the National Institutes of Health.

Analysis
Follow-up issues:

- 21 patients had a device implanted but 1 patient had not completed postoperative polysomnography by the time of data analysis and manuscript submission and was therefore excluded from data analysis.
- Clinical follow-up after device implantation included a postoperative examination within 1 to 2 weeks, device activation and initiation of therapy 1 month after implantation, and follow-up polysomnography testing and clinical assessment 2 to 6 months after implantation.
- Mean postoperative sleep laboratory testing was completed 91.4 ± 45.4 days (range, 58-222 days) after device implantation.
- Mean interval from implantation to most recent office visit was 232.6 ± 101.9 days (range, 109-400 days). The variability in clinical follow-up was primarily a manifestation of the month and year the implant was performed, as patients implanted earlier had a longer course of postoperative evaluation.
- Objective device data for 1 patient were not available at the time of manuscript submission as further postoperative clinic assessment had been deferred due to a new cancer diagnosis requiring frequent chemotherapy treatments

Study design issues: Data collected from the chart review included age, sex, pre- and postoperative BMI, history of OSA treatment, and any procedure- and therapy-related complications. Self-reported data consisted of pre- and postoperative ESS. Mean nightly hours of therapy use were obtained through device interrogation during routine outpatient follow-up. Sleep study data collected included pre- and postoperative AHI and lowest oxygen saturation (LSAT).

Study population issues: 55% (11/20) of patients also had prior intolerance or inadequate effectiveness with oral appliance therapy. 50% (10/20) had previously undergone upper airway reconstructive surgery, including uvulopalatopharyngoplasty, genioglossus advancement, hyoid suspension, expansion pharyngoplasty, and functional nasal surgery. Cumulatively, 35% (7/20) failed to achieve adequate benefit with both oral appliance therapy and upper airway reconstructive surgery.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 20

Outcome measures (mean ± SD)
<table>
<tr><th></th><th>Pre-operative</th><th>Post-operative</th><th>p value</th></tr>
<tr><td>ESS</td><td>10.3 ± 5.2</td><td>6.0 ± 4.4</td><td><0.01</td></tr>
<tr><td>AHI</td><td>33.3 ± 13.0</td><td>5.1 ± 4.3</td><td><0.0001</td></tr>
<tr><td>LSAT</td><td>79.8% ± 6.8 %</td><td>82.2% ± 5.2%</td><td>NS</td></tr>
<tr><td>Total sleep time SpO_2<90% (min)</td><td>15.5 ± 21.4</td><td>14.1 ± 22.0</td><td>NS</td></tr>
</table>
AHI
• AHI<5: 70% (14/20) of patients
• AHI<10: 85% (17/20)
• AHI<15: 95% (19/20)
The patient without good clinical response (AHI>15) also had poor tongue movement with stimulation, demonstrating mixed coactivation of both retractor and protrusor muscles.

Objective adherence
Rate of device voluntary use: mean 7.0±2.2 h/night</td><td>• Postoperative seroma at an incision site in the immediate postoperative period: 2/20
One seroma occurred at the sensing lead incision 1 week after surgery and the other at the implantable pulse generator incision 4 weeks after surgery. Both resolved uneventfully with in-office percutaneous needle drainage.
• Prolonged incisional discomfort: 1/20
The patient reported 6 weeks of pain at the sensing lead site when lying on the right side that required prescription of opioid pain medication.

• Dry mouth in the morning: 3/20
• Mild tongue abrasion after device activation due to the tongue rubbing against the maxillary teeth during protrusion: 1/20
The therapy-related side effects spontaneously resolved.</td></tr>
<tr><td colspan="2">Abbreviations used: AHI, apnoea-hypopnoea index; BMI, body mass index; PAP, positive airway pressure; ESS, Epworth sleepiness scale; IPG, implantable pulse generator; LSAT, lowest oxygen saturation; NS, not statistically significant; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; SD, standard deviation.</td></tr>
</table>

Efficacy

Apnoea-hypopnoea index (AHI)

In a systematic review and meta-analysis of 200 patients, there was a statistically significant decrease in the AHI (a normal AHI is less than 5 per hour). At 3-, 6-, and 12-month follow-up the mean differences from baseline were −23.94 (95% confidence interval [CI] −31.45 to −16.43, 34 patients), −25.60 (95% CI −31.18 to −20.01, 60 patients) and −17.51 (95% CI −20.69 to −14.34, 170 patients) respectively ($p<0.001$ for all time points). [1]

In a prospective case series of 126 patients, there was a statistically significant decrease in the mean AHI ± standard deviation (SD) from 32.0±11.8 at baseline to 15.3±16.1 at 1 year ($p<0.001$). [2]

In a randomised controlled therapy-withdrawal trial of 46 'responders' from the prospective case series of 126 patients (23 therapy-maintenance responders compared to 23 therapy-withdrawal responders), there was a statistically significant increase in the mean AHI from 7.6 at 1-year follow-up (before randomisation into the trial) to 25.8 at 1 week after randomisation, in the group where the device was turned off for 1 week ($p<0.001$). There was no statistical difference in mean AHI within the therapy-maintenance group, who continued to use the device (7.2 compared to 8.9).[2] At 18-month follow-up, the mean AHI scores were 9.6 in the therapy-maintenance group and 10.7 in the group who had the device turned off for 1 week ($p<0.05$ for the differences compared with baseline within groups).[4] There was a statistically significant difference between the therapy-withdrawal group and the therapy-maintenance group for change in mean AHI, from assessment at 1 year to assessment at the end of the therapy-withdrawal study ($p<0.001$).[2]

In a follow-up study of 98 patients from the prospective case series of 126 patients, there was a statistically significant decrease in the mean AHI (±SD) from 30.4±10.4 at baseline to 11.5±13.9 at 3-year follow-up (change 18.8, 95% CI 16.1 to 21.6, $p<0.001$). Treatment success at 3 years (defined as an AHI decrease of more than 50%, to a score of less than 20) was 74% (73/98). [3]

In a prospective case series of 60 patients, there was a statistically significant decrease in the mean AHI ± standard deviation from 31.2±13.2 at baseline to 12.0±9.8 at 6-month follow-up ($p<0.001$). The proportion of responders (AHI<20 with at least 50% reduction) was 63% after 6 months.[5]

In a prospective case series of 46 patients, there was a statistically significant decrease in the mean AHI ± SD from 34.9±22.5 at baseline to 25.4±23.1 at 6-month follow-up ($p=0.004$). The proportion of responders (AHI<20 with at least 50% reduction) was 35% (15/43) after 6 months.[6]

In a prospective case series of 31 patients, there was a statistically significant decrease in the mean AHI± standard deviation from 32.9± 11.2 at baseline to 7.1±5.9 at 1-year follow-up (p<0.001).[7]

In a retrospective case series of 20 patients, there was a statistically significant decrease in the mean AHI± standard deviation from 33.3± 13.0 at baseline to 5.1±4.3 within 6 months after implantation (p<0.0001).[8]

Oxygen desaturation index (ODI)

In the systematic review and meta-analysis of 200 patients, there was a statistically significant decrease in the ODI (defined as the number of times per hour of sleep that the blood oxygen level drops by 4 or more percentage points from baseline). At 3-, 6-, and 12-month follow-up the mean differences from baseline were −10.04 (CI −16.31 to −3.78, 34 patients), −11.68 (95% CI −17.16 to −6.19, 60 patients) and −13.73 (95% CI −16.87 to −10.58, 170 patients) respectively (p<0.01 at 3 months and p<0.001 at 6 and 12 months). [1]

In the prospective case series of 126 patients, there was a statistically significant decrease in the mean ODI ± standard deviation from 28.9±12.0 at baseline to 13.9±15.7 at 1 year (p<0.001). [2]

In the randomised controlled therapy-withdrawal trial of 46 responders from the prospective case series of 126 patients (23 therapy-maintenance responders compared to 23 therapy-withdrawal responders), there was a statistically significant increase in the mean ODI from 6.0 at 1-year follow-up before randomisation to 23.0 a week after randomisation in the therapy-withdrawal group (p<0.001); there was no statistical difference within group in the therapy-maintenance group (6.3 compared to 8.0). After 18-month follow-up, the mean ODI scores were 8.6 in the therapy-maintenance group and 9.1 in the group who had the device turned off for 1 week (p<0.05 for the differences versus baseline within groups).[4] With respect to the change in mean ODI from the assessment at 1 year to the assessment at the end of the therapy-withdrawal study, there was a statistically significant difference between the therapy-withdrawal group and the therapy-maintenance group (p<0.001).[2]

In the 3-year follow-up study of 98 patients from the prospective case series of 126 patients, there was a statistically significant decrease in the mean ODI from 27.1±10.8 at baseline to 9.1±11.7 at 3 years (change 18.0, 95% CI 15.5 to 20.4, p<0.001).[3]

In the prospective case series of 60 patients, there was a statistically significant decrease in the mean ODI±SD from 27.6±16.4 at baseline to 13.5±10.7 at 6-month follow-up (p<0.001). [5]

In the prospective case series of 46 patients, there was a statistically significant decrease in the mean ODI ± SD from 32.4± 22.3 at baseline to 23.6±22.3 at 6-

month follow-up (p=0.006). The proportion of ODI responders (ODI with at least 50% reduction) was 40% (17/43) after 6 months.[6]

In the prospective case series of 31 patients, there was a statistically significant decrease in the mean ODI± SD from 30.7± 14.0 at baseline to 9.9±8.0 at 1-year follow-up (p=0.004).[7]

Epworth sleepiness scale (ESS)

In the systematic review and meta-analysis of 200 patients, there was a statistically significant decrease in the ESS (score range 0 to 24 with higher scores indicating more daytime sleepiness). At 3-, 6-, and 12-month follow-up the mean differences from baseline were -4.17 (CI −6.45 to −1.90, 34 patients), −3.82 (95% CI −5.37 to −2.27, 60 patients) and −4.42 (95% CI −5.39 to −3.44, 170 patients) respectively (p<0.001 for all time points). [1]

In the prospective case series of 126 patients, there was a statistically significant decrease in the mean ESS score ± standard deviation from 11.6±5.0 at baseline to 7.0±4.2 at 1 year (p<0.001). [2]

In the 3-year follow-up study of 98 patients from the prospective case series of 126 patients, there was a statistically significant decrease in the mean ESS score ± standard deviation from 11.4±5.1 at baseline to 7.0±5.0 at 3 years (change 4.5, 95% CI 3.3 to 5.4, p<0.001).[3]

In the randomised controlled therapy-withdrawal trial of 46 responders from the prospective case series of 126 patients (23 therapy-maintenance patients compared to 23 therapy-withdrawal patients), the ESS scores at follow-up were all statistically significantly better than baseline in the therapy-maintenance group (11.2 at baseline, 5.9 at 1 year before randomisation, 5.6 at 1 year after randomisation and 6.0 at 18 months, p<0.05 versus baseline). In the therapy-withdrawal group the ESS scores were statistically significantly better than baseline (11.3) at 1-year before randomisation and after 18 months (6.9 and 8.0 respectively; p<0.05 versus baseline) but not after the device had been turned off for 1 week (10.0).[4]

In the prospective case series of 60 patients, there was a statistically significant decrease in the mean ESS score ± standard deviation from 12.8±5.4 at baseline to 7.0±4.5 at 6-month follow-up (p<0.001). [5]

In the prospective case series of 46 patients, there was a statistically significant decrease in the mean ESS score ± standard deviation from 12.0±4.8 at baseline to 8.3±4.4 at 6-month follow-up (p<0.001).[6]

In the prospective case series of 31 patients, there was a statistically significant decrease in the mean ESS score± standard deviation from 12.6± 5.6 at baseline to 5.9±5.2 at 1-year follow-up (p=0.006).[7]

In the retrospective case series of 20 patients, there was a statistically significant decrease in the mean ESS score from 10.3± 5.2 at baseline to 6.0±4.4 within 6 months after implantation (p<0.01).[8]

Functional Outcomes of Sleep Questionnaire (FOSQ)

In the prospective case series of 126 patients, there was a statistically significant increase in the mean FOSQ score (ranging from 5 to 20 with higher scores indicating better subjective sleep quality) from 14.3±3.2 at baseline to 17.3±2.9 at 1-year follow-up (p<0.001). [2]

In the follow-up study of 98 patients from the prospective case series of 126 patients, there was a statistically significant increase in the mean FOSQ score from 14.6±3.0 at baseline to 17.4±3.5 at 3-year follow-up (change −2.7, 95% CI −3.4 to −1.9, p<0.001).[3]

In the randomised controlled therapy-withdrawal trial of 46 responders from the prospective case series of 126 patients (23 therapy-maintenance patients compared to 23 therapy-withdrawal patients), the FOSQ scores at follow-up were all statistically significantly better than baseline in the therapy-maintenance group (15.1 at baseline, 17.9 at 1 year before and after randomisation and 18.0 at 18 months, p<0.05 versus baseline). In the therapy-withdrawal group the FOSQ scores were statistically significantly better than baseline at 1-year before randomisation and after 18 months (17.0 and 17.1 respectively; p<0.05 versus baseline) but not after the device had been turned off for 1 week (15.0).[4]

In the prospective case series of 60 patients, there was a statistically significant increase in the mean FOSQ score ± standard deviation from 13.2±3.5 at baseline to 16.9±2.9 at 6-month follow-up (p<0.001). [5]

Proportion of sleep time with oxygen saturation < 90%

In the prospective case series of 126 patients, there was a statistically significant decrease in the mean proportion of sleep time with oxygen saturation <90% ± standard deviation from 8.7%±10.2% at baseline to 5.9%±12.4% at 1 year (p=0.01). [2]

In the follow-up study of 98 patients from the prospective case series of 126 patients, the decrease in the mean proportion of sleep time with oxygen saturation <90% was not statistically significant (change 2.2%, 95% CI −0.1 to 4.5, p=0.06).[3]

In the randomised controlled therapy-withdrawal trial of 46 responders from the prospective case series of 126 patients (23 therapy-maintenance responders compared to 23 therapy-withdrawal responders), there was a statistically significant improvement in the mean proportion of sleep time with oxygen saturation < 90% from 7.4%±8.3% at baseline to 4.2%±6.2% a week after randomisation in the therapy-maintenance group (p<0.05 versus baseline within

group); there was no statistical difference within group in the therapy-withdrawal group (5.6%±4.4% compared to 7.5%±10.5%). After 18-month follow-up, the proportions of sleep time with oxygen saturation<90% were 7.6%±17.8% in the therapy-maintenance group and 1.7%±6.2% in the group who had the device turned off for 1 week at 1-year follow-up ($p<0.05$ for the differences versus baseline in the therapy-withdrawal group).[4]

In the prospective case series of 60 patients, there was no statistically significant difference in the mean proportion of sleep time with oxygen saturation <90% between rates at baseline and rates at 6-month follow-up (10.7% versus 7.1%, $p=0.26$). [5]

Arousal index (AI)

In the randomised controlled therapy-withdrawal trial of 46 responders from the prospective case series of 126 patients (23 therapy-maintenance responders compared to 23 therapy-withdrawal responders), there was a statistically significant improvement in the mean AI from 30.9±13.5 at baseline to 13.2±9.9 a week after randomisation and to 14.8±10.4 at 18 months in the therapy-maintenance group ($p<0.05$ versus baseline within group at all time points); after randomisation and after the device had been turned off for a week, there was no statistically significant difference within group from baseline in the therapy-withdrawal group (26.2±14.6 compared to 30.9±16.4). However, after 18-month follow-up, the AI score was 17.2±9.9 ($p<0.05$ for the difference versus baseline).[4]

In the prospective case series of 46 patients, there was a statistically significant decrease in the mean AI ± standard deviation from 42.7± 19.4 at baseline to 31.6±20.3 at 6-month follow-up ($p<0.001$).[6]

Therapy use

In the systematic review and meta-analysis of 200 patients, 3 studies reported data on therapy use that showed use on more than 85% of nights (range 86% to 96%) during 5.4 to 7.5 hours per night.[1]

In the follow-up study of 98 patients from the prospective case series of 126 patients, the rates of self-reported therapy use were 86% (100/116) at 1-year and 81% (94/116) at 2- and 3-year follow-up.[3]

In the prospective case series of 60 patients, the mean therapy use 6 months after implantation was 42.9±11.9 h/ week (range 9 to 64h/week). [5]

In the prospective case series of 31 patients, the mean therapy use was 6.6±2.7 h/ night at 1-year follow-up.[7]

In the retrospective case series of 20 patients, the mean therapy use was 7.0± 2.2 h/night within 6 months after implantation.[8]

Snoring

In the follow-up study of 98 patients from the prospective case series of 126 patients, the rates of bed partner-reported 'no snoring' or 'soft snoring' were 17% (18/108) at baseline, 86% (89/103) at 1-year follow-up and 80% (78/97) at 3-year follow-up.[3]

In the randomised controlled therapy-withdrawal trial of 46 responders from the prospective case series of 126 patients, snoring severity measured by the percentage of soft or no snoring reported by self and bed partner improved in both groups from baseline to 12 months. The percentage of soft or no snoring significantly decreased with therapy withdrawal and returned to treatment baseline at 18 months.[4]

Sleep apnoea quality of life index (SAQLI)

In the prospective case series of 46 patients, there was a statistically significant improvement in the mean SAQLI from 4.3± 1.0 at baseline to 4.7±1.2 at 6-month follow-up (p=0.019).[6]

Safety

Tongue weakness/ paresis

Transient ipsilateral hemi-tongue paresis was reported in 15% (2/13) of patients in a prospective case series of 13 patients from a systematic review and meta-analysis of 200 patients. [1]

Temporary tongue weakness was reported in 18% (23/126) of patients in a prospective case series of 126 patients within 1 year after the procedure.[2, 3]

Acute tongue numbness was reported in 1 patient in a prospective case series of 60 patients. It resolved after 2 months.[5]

Paresis was reported in 11% (5/46) of patients within 30 days of implantation in a prospective case series of 46 patients; all cases resolved spontaneously.[6]

Tongue soreness/ abrasion

Tongue abrasion was reported in 25% (32/126) of patients in the prospective case series of 126 patients within 3 years of the procedure. In 9 patients, a tooth guard was used to resolve the tongue soreness or abrasion related to the device.[2, 3]

Mild tongue abrasion was reported in 1 patient in a retrospective case series of 20 patients after device activation caused by the tongue rubbing against the maxillary teeth during protrusion. [8]

Dysarthria

Dysarthria was reported in 1 patient in the prospective case series of 60 patients. It resolved after 2 months. In the same study, speech difficulty was reported in 1 patient; this was resolved by reprogramming the stimulation energy field parameters. [5]

Bleeding

Bleeding was reported in 3% (2/60) of patients during tunnelling of the stimulation lead from the neck incision to the device pocket in the prospective case series of 60 patients. [5]

Bleeding was reported in 1 patient within 30 days of implantation in the prospective case series of 46 patients. This was caused by a hypertensive crisis and surgical intervention was needed; hypertension was treated with medication. In the same study, haematoma was reported in 7% (3/46) of patients. One of the 2 cases classified as non-serious occurred within 30 days of implantation and the other occurred more than 30 days after implantation. The third case was classified as a serious event and occurred within 30 days of implantation.[6]

Rupture of vein was reported in 6% (2/31) of patients during cervical tunnelling in a prospective case series of 31 patients; 1 of the patients needed 1 further cervical incision.[7]

Seroma

Seroma at an incision site was reported in 10% (2/20) of patients immediately after the procedure in the retrospective case series of 20 patients. One seroma occurred at the sensing-lead incision 1 week after surgery and the other occurred at the implantable pulse-generator incision 4 weeks after surgery. Both resolved uneventfully with percutaneous needle drainage.[8]

Headache

Headache was reported in 6% (8/126) of patients in the prospective case series of 126 patients within 1 year of the procedure.[2, 3]

Infection

Infection was reported in 1 patient in a prospective case series of 22 patients reported in the systematic review and meta-analysis of 200 patients; the device was removed. [1]

Mild infection was reported in 1 patient in the prospective case series of 126 patients within 1 year of the procedure. In the same study, skin cellulitis was reported in 1 patient within 1 year of the procedure. [2, 3]

Infection was reported in 9% (4/46) of patients within 30 days of implantation in a prospective case series of 46 patients.[6]

Dry mouth

Dry mouth was reported in 13% (16/126) of patients in the prospective case series of 126 patients within 3 years of the procedure.[3]

Dry mouth in the morning was reported in 15% (3/20) of patients in the retrospective case series of 20 patients.[8]

Pain

Pain and swelling at the neck incision site was reported in 1 patient in the prospective case series of 22 patients reported in the systematic review and meta-analysis of 200 patients; this resolved after antibiotic treatment. [1]

Mechanical pain associated with the presence of the device was reported in 10% (12/126) of patients in the prospective case series of 126 patients within 3 years of the procedure.[3]

Discomfort due to electrical stimulation was reported in 56% (70/126) of patients in the prospective case series of 126 patients within 3 years of the procedure. In the same study, discomfort related to incisions was reported in 29 % (37/126) of patients and discomfort not related to incisions was reported in 27% (34/126) of patients within 3 years after the procedure. [3]

Pain related to the incision was reported in 8% (5/60) of patients after the procedure in the prospective case series of 60 patients. In the same study, painful stimulation sensation after therapy activation was reported in 5% (3/60) of patients; in 2 patients, pain resolved without intervention and the other patient was still monitored at the time the paper was being written.[5]

Pain was reported in 41% (19/46) patients in the prospective case series of 46 patients (7 patients reported non-serious pain within 30 days of implantation, 12 reported it more than 30 days after implantation, 3 patients reported serious pain: 1 case within 30 days and 2 cases more than 30 days after implantation). [6]

Prolonged incisional discomfort was reported in 1 patient in the retrospective case series of 20 patients. The patient reported 6 weeks of pain at the sensing lead site when lying on the right side that required opioid pain medication.[8]

Paraesthesia

Paraesthesia was reported in 13% (6/46) of patients (within 30 days of implantation in 5 patients, and more than 30 days after implantation in 1 patient) in the prospective case series of 46 patients.[6]

Swelling

Swelling was reported in 1 patient in the prospective case series of 13 patients reported in the systematic review and meta-analysis of 200 patients. [1]

Psychological disturbance

Psychological disturbance was reported in 1 patient in a prospective case series of 31 patients reported in the systematic review and meta-analysis of 200 patients; the patient was readmitted to hospital because of a combination of self-discontinuation of antidepressant medications and prescription of opioids for pain control after the procedure. [1]

Device migration

Device migration more than 30 days after implantation was reported in 1 patient in the prospective case series of 46 patients. [6]

Device revision

Cuff dislodgement was reported in 2 patients in the prospective case series of 31 patients, and in 1 patient in a prospective case series of 21 patients, from the systematic review and meta-analysis of 200 patients; all 3 patients needed a new procedure to replace it.[1]

Device revision was reported in 2% (2/126) of patients in the prospective case series of 126 patients within 1 year of the procedure.[2]

Lead revision was needed after 1 patient reported no stimulation 29 days after implantation in the prospective case series of 46 patients. [6]

Device removal

Device removal was reported in 4 patients in the prospective case series of 31 patients, and in 2 patients in the prospective case series of 21 patients, from the systematic review and meta-analysis of 200 patients.[1]

Device removal was also reported in 2 patients 1 to 3 years after the procedure, in the prospective case series of 126 patients. The reasons for removal were insomnia for 1 patient and device-unrelated septic arthritis for the other patient. [3]

Device functionality complaint

Temporary internal device usability or functionality complaint was reported in 13% (17/126) of patients within 3 years of the procedure in the prospective case series of 126 patients. In the same study, temporary external device usability or functionality complaint was reported in 19% (24/126) of patients within 3 years of the procedure. [3]

Device malfunction

Leads breaking was reported in 15% (2/13) of patients in the prospective case series of 13 patients from the systematic review and meta-analysis of 200 patients. [1]

Defective implanted pulse-generator connector was reported in 1 patient in the prospective case series of 13 patients from the systematic review and meta-analysis of 200 patients. [1]

Other

Other complications reported in the systematic review and meta-analysis of 200 patients and not already described above included postoperative stiffness, sore throat, stitch abscess, local swelling, fever, and lack of tongue response to stimulation. [1]

Validity and generalisability of the studies

- The only randomised controlled trial included in table 2 was a study were patients were randomised to a withdrawal of treatment. The patients selected for the study were responders from the STAR trial and the study only included 46 patients.[2,4]
- The longest follow-up was 3 years[3].
- The inclusion and exclusion criteria for the studies included in table 2 were generally highly specific. Therefore the patients included in the studies may not be representative of the population with moderate to severe OSA.
- There is likely to be some patient overlap between the studies included in table 2. The Strollo (2014) study[2] included in table 2 is also included in the Certal (2014) systematic review and meta-analysis[1] and the Woodson (2016)[3] paper reports data on a 3-year follow-up of the Strollo (2014) study[2] patients. The Woodson (2014) study[4] reports on the 18-month follow-up of the randomised controlled withdrawal therapy study (which also includes patients from the Strollo (2014) study[2]). The patients included in the Heiser (2017b)[7] study are also likely to be also included in the Heiser (2017a)[5] study.

- There are various devices used for hypoglossal nerve stimulation in the studies included in table 2.

Existing assessments of this procedure

- HTA-centrum, Region Västra Götaland, Sweden published a Health Technlogy Assessment on Hypoglossal nerve stimulation (HGNS) for treatment of obstructive sleep apnea in 2015[9]. It stated: “This report assessing the evidence for hypoglossal nerve stimulation therapy in patients with obstructive sleep apnoea refractory to continuous positive airway pressure shows that the therapy may substantially reduce important measures of OSA severity. Patient selection appears to be essential to the success of therapy. Severe device-related adverse events are rare. The hypoglossal nerve stimulation treatment is expensive and further studies with long-term follow-up are needed”.

- The Ludwig Boltzmann Institute for Health Technology Assessment published a decision support document for Upper airway stimulation for moderate-to-severe sleep apnoea in 2016[10]. It stated: “The inclusion in the catalogue of benefits is currently not recommended. The current evidence is not sufficient to prove that hypoglossal nerve stimulation for treating moderate-to-severe obstructive sleep apnea is more effective and equally safe than no treatment. New study results will potentially influence the effect estimate considerably. The re-evaluation is recommended in 2018”.

- The Australian Health Policy Advisory Committee on Technology (HealthPACT) published a brief on Upper Airway Stimulation for Moderate-to-Severe Sleep Apnoea in March 2015[11]. It stated: “The evidence-base supporting the use of upper airway stimulation to treat obstructive sleep apnoea was weak, consisting of case series and one study where patients were randomised to a withdrawal of treatment. This latter study demonstrated a worsening of both objective and subjective measures of sleep and breathing after treatment withdrawal. However, the study was small and participants were recruited from the industry-sponsored, uncontrolled STAR study and, therefore, highly selective and not representative of the target population. Based on the lack of safety and clinical effectiveness evidence in the appropriate population, it is unlikely this device will diffuse into the jurisdictions within the next one to three years. It is therefore recommended that no further research on behalf of HealthPACT is warranted at this time”.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Radiofrequency ablation of the soft palate for snoring. NICE interventional procedure guidance 476 (2014). Available from https://www.nice.org.uk/guidance/ipg476
- Soft-palate implants for obstructive sleep apnoea. NICE interventional procedure guidance 241 (2007). Available from https://www.nice.org.uk/guidance/ipg241
- Soft-palate implants for simple snoring. NICE interventional procedure guidance 240 (2007). Available from https://www.nice.org.uk/guidance/ipg240

Technology appraisals

- Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. NICE technology appraisal guidance 139 (2008). Available from https://www.nice.org.uk/guidance/ta139

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE did not receive any completed submission.

Issues for consideration by IPAC

- Ongoing studies:

  - NCT02293746. Inspire® Upper Airway Stimulation (UAS) System German Post-Market Study. Prospective case series; Germany; estimated enrolment: 60; estimated completion date: April 2016.

  - NCT01161420. Stimulation Therapy for Apnea Reduction (Www.theSTARtrial.Com) (STAR), Study type, case series; location, Multicentre (United States, Belgium, France, Germany, Netherlands); enrolment, 929; estimated completion date, March 2017.

  - NCT02907398. Adherence and Outcome of Upper Airway Stimulation (UAS) for OSA International Registry. Observational cohort study [Patient Registry]. United States. Estimated enrolment: 2500. Start date: September 2016. Estimated primary completion date: September 2018.

  - NCT02344108. A Pilot Study to Evaluate the Safety and Efficacy of the Hypoglossal Nerve Stimulator in Adolescents With Down Syndrome and Obstructive Sleep Apnea. Case series. Recruiting. United States. Estimated enrolment: 21; estimated completion dates: February 2019.

- NCT02263859. Targeted Hypoglossal Neurostimulation Study #3 (THN3). Randomised, open-label, parallel assignment trial; Recruiting; United States, Belgium, France, Germany, Israel, Portugal; estimated enrolment: 141; estimated primary completion date: October 2016; estimated final completion date: May 2021.

- NCT02413970. Inspire® Post-Approval Study / Protocol Number 2014-001.Case series. Recruiting. United States. Estimated enrolment: 127. Estimated study completion date: December 2021.

- NCT03048604. BiLAteral Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnoea (BLAST OSA). Prospective case series. Study not yet open for recruitment. Countries not reported. Estimated enrolment: 25. Estimated completion date: March 2018.

- One of the devices (HGNS [Apnex Medical]) used in the studies included in the overview is no longer on the market.

- There is a new type of device used for hypoglossal nerve stimulation which claims to be less invasive, without battery and less complex to implant (the Nyxoah system). However there is no published evidence on this device included in this overview.

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11. Health Policy Advisory Committee on Technology (2015) Technology Brief Update Upper Airway Stimulation for Moderate-to-Severe Sleep Apnoea. https://www.health.qld.gov.au/__data/assets/pdf_file/0034/431998/wp097update.pdf

Appendix A: Additional papers on hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Diercks G R, Keamy D, Kinane T B, et al. (2016) Hypoglossal Nerve Stimulator Implantation in an Adolescent With Down Syndrome and Sleep Apnea. Pediatrics 137(5).	Single case report FU=5 months	Hypoglossal nerve stimulator therapy was well tolerated and effective, resulting in significant improvement in the patient's OSA. Five months after implantation, the patient's tracheotomy was successfully removed and he continues to do well with nightly therapy.	Studies with more patients or longer follow-up are included.
Eastwood P R, Barnes M, Walsh J H et al. (2011) Treating obstructive sleep apnea with hypoglossal nerve stimulation. Sleep 34(11), 1479-86.	Prospective case series n=21 FU=6 months	This case-study demonstrates the feasibility of long-term HGNS Therapy for treating OSA.	Studies with more patients or longer follow-up are included. This study is included in the Certal (2014) systematic review and meta-analysis.
Heiser C, Maurer J T, and Steffen A (2016) Functional outcome of tongue motions with selective hypoglossal nerve stimulation in patients with obstructive sleep apnea. Sleep & Breathing 20(2), 553-60.	Case series n=14 FU=6 months	The average apnea-hypopnea index (AHI) was reduced from 32.5 +/- 14.2/h before surgery to 17.9 +/- 23.3/h at M02 and 14.1 +/- 19.8/h at M06. An increased reduction in AHI was found in bilateral protrusion and right protrusion group.	Studies with more patients or longer follow-up are included.
Kezirian E J, Goding G S, Jr, Malhotra A, O'Donoghue F J et al. (2014) Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. Journal of Sleep Research 23(1), 77-83.	Prospective case series n=32 FU=1 year	There was a significant improvement from baseline to 12 months in apnea-hypopnea index and Functional Outcomes of Sleep Questionnaire score and other polysomnogram and symptom measures. Outcomes were stable compared with 6 months following implantation. 3 serious device-related adverse events occurred: an infection requiring device removal; and two stimulation lead cuff dislodgements requiring replacement. There	Studies with more patients or longer follow-up are included. This study is included in the Certal (2014) systematic review and meta-analysis.

		were no significant adverse events with onset later than 6 months following implantation. Hypoglossal nerve stimulation demonstrated favourable safety, feasibility and efficacy.	
Kezirian E J, Boudewyns A, Eisele D W, Schwartz A R, Smith P L, Van de Heyning , P H, De Backer , and W A (2010) Electrical stimulation of the hypoglossal nerve in the treatment of obstructive sleep apnea. Sleep Medicine Reviews 14(5), 299-305	Case series n=8 FU=6 months	The results demonstrated an improvement in upper airway collapsibility and obstructive sleep apnea severity. Future research, including optimization of device features and stimulation parameters as well as patient selection, is necessary to make hypoglossal nerve stimulation a viable alternative to positive airway pressure therapy and upper airway surgical procedures.	Studies with more patients or longer follow-up are included.
Murphey A W, Baker A B, Soose R J et al. (2016) Upper airway stimulation for obstructive sleep apnea: The surgical learning curve. Laryngoscope 126(2), 501-6	Retrospective review n=126 patients from the STAR trial	Surgical time for implantation of the UAS system decreased significantly after the first 5 implants and then stabilized. The rate of surgical complications did not decrease with surgeon experience, although this may be attributable to the low overall rate of serious surgical complications and low number of implants at some centres. Level of evidence: 4.	The objective of the study was to determine the effect of surgeon experience with an upper stimulation system on surgical time and complication rates. The results of the STAR trial are included in Table 2.
Mwenge G B, Rombaux P, Dury M et al. (2013) Targeted hypoglossal neurostimulation for obstructive sleep apnoea: a 1-year pilot study. European Respiratory Journal 41(2), 360-7	Case series n=14 FU=1 year	At 12 months, the AHI decreased from 45+/-18 to 21+/-17, a 53% reduction ($p<0.001$). The 4% oxygen desaturation index fell from 29+/-20 to 15+/-16 and the arousal index from 37+/-13 to 25+/-14, both ($p<0.001$). The Epworth sleepiness scale decreased from 11+/-7 to 8+/-4 ($p=0.09$). THN was neither painful nor awakened patients, who all complied with therapy. There were 2 transient tongue paresis. The present study represents the longest study of any hypoglossal neurostimulation reported to date. We conclude that THN is safe and effective to treat OSA in patients not compliant with CPAP.	Studies with more patients or longer follow-up are included. This study is included in the Certal (2014) systematic review and meta-analysis.
Ong A A, Murphey A W, Nguyen S A et al. (2016) Efficacy of Upper Airway Stimulation on Collapse Patterns Observed during Drug-Induced	Retrospective review n=126 FU=1 year	Drug-induced sedation endoscopy is an efficient and safe method for determining UAS eligibility and has the potential to identify UAS non-responders. Most patients had	The objective of the study was to describe upper airway collapse patterns observed on drug-induced sedation endoscopy (DISE)

Sedation Endoscopy. Otolaryngology - Head & Neck Surgery 154(5), 970-7		multilevel airway collapse, illustrating the limitations of single-level upper airway surgery in treating obstructive sleep apnoea. Upper airway stimulation is effective therapy for most patients with multilevel airway collapse; however, patients with complete anterior-posterior or lateral soft palate and/or epiglottic collapse may be at increased risk of therapy failure.	during screening for a clinical trial and to evaluate the impact of collapse patterns found on preoperative DISE on response rates to upper airway stimulation therapy. The results of the STAR trial are included in Table 2
Ong A A, O'Brien T X, Nguyen S A et al. (2016) Implantation of a defibrillator in a patient with an upper airway stimulation device. Laryngoscope 126(2), E86-9	Single case report FU=2.5 years	This is the first reported case of simultaneous use of a UAS and an ICD, and we report no untoward device interference between the 2 implantable devices.	Studies with more patients or longer follow-up are included.
Schwartz A R, Bennett M L, Smith P L et al. (2001) Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. Archives of Otolaryngology -- Head & Neck Surgery 127(10), 1216-23	Case series n=8 FU=6 months	The findings demonstrate the feasibility and therapeutic potential for hypoglossal nerve stimulation in obstructive sleep apnoea.	Studies with more patients or longer follow-up are included.
Soose R J, Woodson B T, Gillespie M B et al. (2016) Upper Airway Stimulation for Obstructive Sleep Apnea: Self-Reported Outcomes at 24 Months. Journal of Clinical Sleep Medicine 12(1), 43-8	Prospective case series n=126 FU=24 months	In a selected group of patients with moderate to severe OSA and body mass index < 32 kg/m^2, hypoglossal cranial nerve stimulation therapy can provide significant improvement in important sleep-related quality-of-life outcome measures and the effect is maintained across a 2-year follow-up period.	Results from a 3-year follow-up of the STAR trial are included in Table 2.
Strohl M, Strohl K, Palomo J M et al. (2016) Hypoglossal nerve stimulation rescue surgery after multiple multilevel procedures for obstructive sleep apnea. American Journal of Otolaryngology 37(1), 51-3	Single case report FU=5 months	The success of this patient's HNS surgery demonstrates that we need to examine where HNS fits into the approach to surgery for OSA. There could be benefit to considering cranial nerve stimulation earlier than conventional approaches for select patients.	Studies with more patients or longer follow-up are included.
Strollo P J, Jr , Gillespie M B, Soose R J et al. (2015) Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18	Prospective case series n=126 FU=18 months	Upper airway stimulation via the hypoglossal nerve maintained a durable effect of improving airway stability during sleep and improved patient reported outcomes (Epworth Sleepiness Scale and Functional Outcomes of	Results from a 3-year follow-up of the STAR trial are included in Table 2.

Months. Sleep 38(10), 1593-8		Sleep Questionnaire) without an increase of the stimulation thresholds or tongue injury at 18 mo of follow-up.	
Van de Heyning , P H, Badr M S, Baskin J Z et al. (2012) Implanted upper airway stimulation device for obstructive sleep apnea. Laryngoscope 122(7), 1626-33	Prospective case series Part 1, n=22 Part 2, n=8 (responders) FU=6 months	In part 1, 20/ 22 enrolled patients (2 exited the study) were examined for factors predictive of therapy response. Responders had both a body mass index <32 and AHI <50 ($p < .05$) and did not have complete concentric palatal collapse. Part 2 patients (n = 8) were selected using responder criteria and showed an improvement on AHI from baseline, from 38.9 +/- 9.8 to 10.0 +/- 11.0 ($p < .01$) at 6 months post-implant. Both ESS and FOSQ improved significantly in part 1 and 2 subjects.	Studies with more patients or longer follow-up are included. This study is included in the Certal (2014) systematic review and meta-analysis.

Appendix B: Related NICE guidance for hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

Guidance	Recommendations
Interventional procedures	**Radiofrequency ablation of the soft palate for snoring. NICE interventional procedure guidance 476 (2014).** 1.1 Current evidence suggests that there are no major safety concerns associated with radiofrequency ablation of the soft palate for snoring. The evidence on the short-term efficacy of the procedure is adequate, although uncertainties remain about its efficacy in the longer term. Therefore this procedure may be used with normal arrangements for clinical governance, consent and audit. 1.2 During the consent process clinicians should, in particular, inform patients of the uncertainty about the procedure's long-term efficacy and of the possible need for further procedures if symptoms recur. 1.3 Patient selection is important: the sound of snoring can arise from several different levels in the upper airway and this procedure should only be used for patients whose snoring has been shown to be caused by abnormal movement of the soft palate and in whom sleep apnoea has been excluded. 1.4 NICE encourages further research into radiofrequency ablation of the soft palate for snoring. This could take the form of data collection, with the specific aim of documenting long-term outcomes and the need for further treatment. **Soft-palate implants for obstructive sleep apnoea. NICE interventional procedure guidance 241 (2007).** 1.1 Current evidence on soft-palate implants for obstructive sleep apnoea (OSA) raises no major safety concerns, but there is inadequate evidence that the procedure is efficacious in the treatment of this potentially serious condition for which other treatments exist. Therefore, soft-palate implants should not be used in the treatment of this condition. **Soft-palate implants for simple snoring. NICE interventional procedure guidance 240 (2007).** 1.1 Current evidence on soft-palate implants for simple snoring raises no major safety concerns. However, the evidence on efficacy is based on small case series only and

	there is a lack of well-controlled and comparative data. Therefore, this procedure should only be used in the context of research. 1.2 Further research should include explicit details of patient selection, and both clinical and quality-of-life outcomes.
Technology appraisals	**Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. NICE technology appraisal guidance 139 (2008)**. 1.1 Continuous positive airway pressure (CPAP) is recommended as a treatment option for adults with moderate or severe symptomatic obstructive sleep apnoea/hypopnoea syndrome (OSAHS). 1.2 CPAP is only recommended as a treatment option for adults with mild OSAHS if: • they have symptoms that affect their quality of life and ability to go about their daily activities, **and** • lifestyle advice and any other relevant treatment options have been unsuccessful or are considered inappropriate. 1.3 The diagnosis and treatment of OSAHS, and the monitoring of the response, should be carried out by a specialist service with appropriately trained medical and support staff.

Appendix C: Literature search for hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	31/01/2017	Issue 1 of 12, January 2017
HTA database (Cochrane)	31/01/2017	Issue 4 of 4, October 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	31/01/2017	sue 11 of 12, November 2016
MEDLINE (Ovid)	31/01/2017	1946 to January Week 3 2017
MEDLINE In-Process (Ovid)	31/01/2017	January 30, 2017
EMBASE (Ovid)	31/01/2017	1974 to 2017 Week 05
PubMed	31/01/2017	n/a
BLIC (British Library)	31/01/2017	n/a

Trial sources searched on 05 12 2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 05 12 2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Sleep Apnea Syndromes/

2 (sleep* adj4 (apnoea* or apnea* or hypopnea* or hypopnoea*)).tw.

3 (((sleep* adj4 disorder*) or sleep-disorder*) adj4 breath*).tw.

4 (OSAHS or OSA or OSAS).tw.

5 1 or 2 or 3 or 4

6 Hypoglossal Nerve/

7 ((hypoglossal or genioglossus) adj4 stimul*).tw.

8 HNS.tw.

9 ((XII or XIIS or twelfth or cranial) adj4 stimul*).tw.

10 Electric Stimulation/ or Electric Stimulation Therapy/

11 (electric* adj4 stimul*).tw.

12 electrotherap*.tw.

13 (((upper adj4 airway*) or upper-airway) adj4 stimul*).tw.

14 UAS.tw.

15 (sleep* adj4 therap* adj4 system*).tw.

16 Implantable Neurostimulators/

17 (implant* adj2 stimul*).tw.

18 or/6-17

19 5 and 18

20 ((inspire adj2 (therapy or stimulat*)) or aura6000 or "HGNS system" or genio).tw.

21 19 or 20

22 animals/ not humans/

23 21 not 22