


Upper Airway Stimulation for Obstructive Sleep Apnea: Patient-Reported Outcomes after 48 Months of Follow-up

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Abstract

Objective. To assess patient-based outcomes of participants in a large cohort study—the STAR trial (Stimulation Therapy for Apnea Reduction)—48 months after implantation with an upper airway stimulation system for moderate to severe obstructive sleep apnea.

Study Design. A multicenter prospective cohort study.

Setting. Industry-supported multicenter academic and clinical setting.

Subjects. Participants (n = 91) at 48 months from a cohort of 126 implanted participants.

Methods. A total of 126 participants received an implanted upper airway stimulation system in a prospective phase III trial. Patient-reported outcomes at 48 months, including Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and snoring level, were compared with preimplantation baseline.

Results. A total of 91 subjects completed the 48-month visit. Daytime sleepiness as measured by ESS was significantly reduced ($P = .01$), and sleep-related quality of life as measured by FOSQ significantly improved ($P = .01$) when compared with baseline. Soft to no snoring was reported by 85% of bed partners. Two patients required additional surgery without complication for lead malfunction.

Conclusion. Upper airway stimulation maintained a sustained benefit on patient-reported outcomes (ESS, FOSQ, snoring) at 48 months in select patients with moderate to severe obstructive sleep apnea.

Keywords

obstructive sleep apnea, cranial nerve, hypoglossal nerve, sleep, device, implant, long term, clinical, apnea hypopnea index, sleep, quality of life

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Obstructive sleep apnea (OSA) is a common disorder, with a prevalence of 5% to 10% of the adult US population. OSA is associated with daytime sleepiness, snoring, poor sleep quality, and an increased risk of cardiovascular disease and motor vehicle accidents.^{1,2} Continuous positive airway pressure (CPAP) is the recognized first-line therapy for the majority of patients with OSA; however, many patients reject CPAP therapy due to

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discomfort, air leaks, failure to improve, nasal blockage, and/or claustrophobia. Low adherence rates of 30% to 60% over time limit the effectiveness of CPAP therapy and result in a significant number of untreated or undertreated patients with symptomatic OSA.^{3,4}

Upper airway surgery is an option for patients with symptomatic OSA who are unwilling or unable to adhere to CPAP therapy. Traditionally, upper airway surgery has consisted of a variety of procedures that either remove redundant upper airway tissues or statically reposition tissues to enlarge the upper airway lumen. These procedures are often painful with a prolonged recovery period. In addition, traditional surgical approaches frequently fail to address the underlying increased collapsibility of the airway that exists in OSA patients.^{5,6}

Initial studies of hypoglossal nerve stimulation in animal models of OSA showed significant reduction in airway collapsibility.^{7,8} Early feasibility trials in humans of several hypoglossal nerve stimulation devices demonstrated significant reduction in apnea-hypopnea index (AHI) as well as improvements in sleep-related quality of life.⁹⁻¹¹ These encouraging findings led to a large multicenter phase III study of an upper airway stimulation (UAS) system—the STAR trial (Stimulation Therapy for Apnea Reduction). The UAS system is a fully implantable system that consists of a stimulation lead attached to the distal hypoglossal nerve, an intercostal sensing lead to detect the respiratory cycle, and a pulse generator on the anterior chest wall inferior to the clavicle. The device is activated by the patient prior to sleep with a handheld remote.

The STAR trial demonstrated a significant reduction in the median AHI at 12 months, from 29.3 to 9.0, with two-thirds (66%) of the implanted participants considered successful responders to therapy by previously published criteria of surgical success (AHI decrease $\geq 50\%$ and overall AHI < 20).¹² Given the results of the STAR trial, the US Food and Drug Administration approved upper airway stimulation in 2014 for use in select patients who meet rigorous inclusion criteria, consisting of moderate to severe OSA (AHI, 20-65), failure of CPAP therapy, body mass index (BMI) ≤ 32 kg/m², and absence of complete circumferential palatal collapse on drug-induced sleep endoscopy.

The present work is based on a multicenter longitudinal observational study of the original 126 subjects implanted with a UAS system as part of the STAR trial. The STAR trial protocol required follow-up polysomnograms (PSGs) at 12 and 18 months postimplantation as well as an optional PSG at 36 months, the results of which have been reported.¹³ In addition, the protocol called for regularly scheduled office follow-up every 6 months for up to 5 years after implantation to evaluate validated secondary outcome measures of clinical effectiveness—namely, the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ), and the Subject and Bed-Partner Snoring Scale—and to assess for potential adverse events related to the device. This study presents the results of these secondary outcome measures 48 months following implantation.

Methods

Study Subjects

The STAR trial multicenter cohort included adults with a history of moderate to severe OSA and intolerance or inadequate adherence to CPAP. The trial was approved by the institutional review board (United States) and medical ethics committee (Europe) in each participating center. An independent Clinical Events Committee and a Data Safety Monitoring Board provided review and adjudication of safety data.

Key study exclusion criteria included BMI > 32 kg/m², neuromuscular disease including hypoglossal nerve palsy or injury, severe cardiopulmonary disorders, active psychiatric disease, and comorbid nonrespiratory sleep disorders that would confound functional sleep-related assessments. Participants who met inclusion/exclusion criteria underwent 3 screening tests: an in-laboratory attended PSG, a surgical consultation visit, and a drug-induced sleep endoscopy. Participants were excluded after the PSG for an AHI < 20 or > 50 events per hour of sleep, for central and/or mixed apnea index $> 25\%$ of the AHI, or for a nonsupine AHI < 10 . Participants were excluded if pronounced anatomic abnormalities would prevent effective use of the device (eg, tonsil size, 3 or 4). Drug-induced sleep endoscopy assessed site and pattern of upper airway collapse under sedation (eg, propofol and/or midazolam) and excluded any participants with observed complete concentric collapse at the level of the velopharynx.

Study Procedures

A total of 126 qualified participants who met preimplant screening criteria underwent device implantation with the Inspire UAS system (Inspire Medical Systems, Maple Grove, Minnesota). Details of the surgical technique are described in a prior publication.¹² The device was activated 1 month after the implant procedure. During the first month of at-home use, participants were encouraged to use the device to acclimate to the sensation and gradually increase the stimulation over a predetermined range to improve snoring and daytime sleepiness. Between 2 and 6 months, ≥ 1 in-laboratory PSG titration studies were conducted to determine more precisely the optimal range of stimulation for maximal AHI reduction. Additional titration studies were performed for some participants after 6 months based on previous titration results and participant feedback.

Study Data

Results have been reported on the primary study outcomes of AHI and oxygen desaturation index based on scheduled follow-up PSGs collected at 12 and 18 months per protocol, with an additional optional PSG at 36 months. The present study focuses on the self-reported patient secondary outcomes collected every 6 months through a total of 48 months to date. Secondary outcome measures include subjective sleepiness and sleep-related quality of life with the validated ESS¹⁴ and the FOSQ.¹⁵ Clinical variables—including BMI, neck circumference, tongue function, speech, swallowing, and

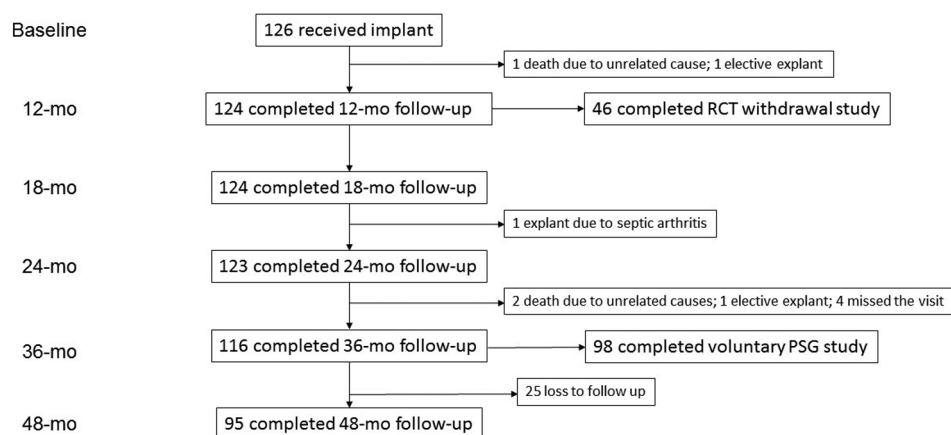


Figure 1. CONSORT diagram. PSG, polysomnography; RCT, randomized controlled trial.

daily device use by self-report—were measured at scheduled visits to assess for any changes over the course of the study. Subjective report of snoring was collected from participants and bed partners' reports with a categorical scale (no snoring, soft snoring, loud snoring, very intense snoring, or bed partner leaves room).

All reported adverse events were reviewed and coded by the Clinical Events Committee. Serious adverse events were defined as any events that led to death, life-threatening illness, permanent impairment, or new or prolonged hospitalization. Adverse events were categorized as procedure related if related to the surgical procedure or device related if secondary to use of the device after therapy activation. Adverse events could also be judged as not fitting in either category.

Statistical Analysis

Ordinal scale data for secondary outcomes (ESS, FOSQ) were tested and found to conform to parametric testing parameters. The paired *t* test was used to evaluate the difference between study baseline and 48 months at the 5% significance level. Adverse events are reported with descriptive statistics.

Results

A total of 95 subjects (75%) of the original 126-patient cohort showed for the 48-month follow-up (**Figure 1**); however, 4 subjects had incomplete data, leaving 91 (73%) for data analysis. At 48 months, 3 subjects in the original cohort had died; 3 had undergone elective explantation of the UAS system; and 25 subjects were lost to follow-up. The cause of death of the 3 subjects has been reported and included a sudden daytime death in a 48-year-old woman with a family history of sudden cardiac death, a 55-year-old man who died from a likely cardiac arrest complicated by a fall down a flight of stairs, and a 64-year-old man who was a victim of a homicide.¹³ Three subjects underwent uneventful explantation of the UAS device, including 1 therapy nonresponder who requested removal before moving away from his study site, 1 therapy responder who developed a septic sternoclavicular joint adjacent to the device, and 1

Table 1. Comparison of Patients Who Completed the 48-Month Visit with Those Lost to Follow-up.^a

Measures	48-mo Visit		P Value
	Completed	Not Completed	
Patients, n	95	25	
Male, n	79	24	
Age, y	55.1 ± 10.5	51.2 ± 8.7	.06
BMI, kg/m ²	28.6 ± 2.7	28.5 ± 1.9	.79
AHI			
Baseline	30.6 ± 11.2	33.4 ± 10.2	.26
12 mo	16.3 ± 17.4	12.8 ± 11.4	.24
Baseline			
ESS	11.4 ± 5.2	12.4 ± 4.8	.35
FOSQ	14.6 ± 3.0	13.1 ± 3.7	.06
36-mo nightly use, %	80	89	.29

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire.

^aValues presented as mean ± SD unless noted otherwise.

therapy responder who suffered from prolonged insomnia complicated by psychological issues.

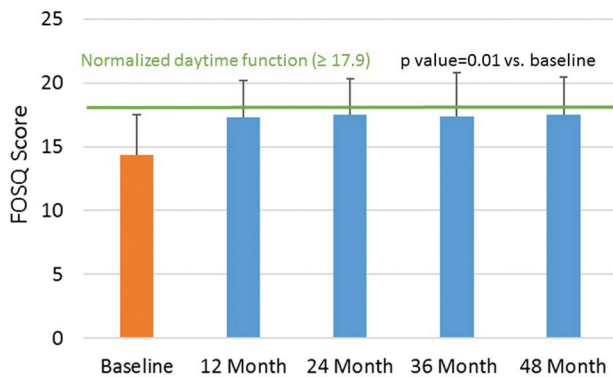
Of the 25 subjects lost to follow-up, 15 missed the 48-month visit; 5 exited the study; and 5 were from 3 study sites that were subsequently closed. The 5 patients who exited the study decided to leave due to relocation (1 patient), inability/unwillingness to adhere to the study follow-up schedule (2 patients), and unavailability (ie, study personnel were unable to contact patient after numerous attempts; 2 patients). Three study sites were closed owing to loss of principal investigator (1 site with 3 patients) and inability of study site to continue participation (2 sites with 1 patient each). In comparing the 95 patients who completed the 48-month follow-up to the 25 who missed the visit (**Table 1**), there was no discernable difference between the groups with regard to therapy response at 12 months and reported nightly use at 36 months. Subjects lost to follow-up

Table 2. Comparison of Baseline Characteristics of Initial STAR Cohort and Those Completing 12- and 48-Month Follow-up.^a

Baseline Characteristics	Preimplant (N = 126)	12 mo (n = 124)	48 mo (n = 91)
Age, y	54 ± 10.2	54.3 ± 10.2	55.7 ± 10.2
BMI, kg/m ²	28.4 ± 2.6	28.5 ± 2.6	28.6 ± 3.2
AHI, events/h	32.0 ± 11.8	31.7 ± 11.6	30.2 ± 11.0

Abbreviation: AHI, apnea-hypopnea index; BMI, body mass index; STAR, Stimulation Therapy for Apnea Reduction.

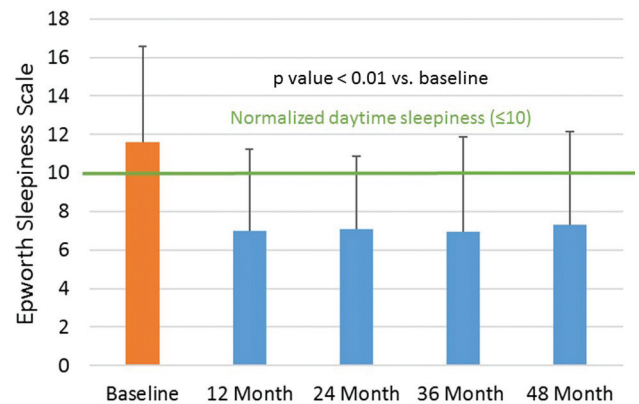
^aValues presented as mean ± SD.

**Figure 2.** Functional Outcome of Sleep (FOSQ) results over time: normal sleep-related quality of life ≥ 17.9 . Results in mean and standard deviation.

had a trend toward younger age and worse sleep-related quality of life at baseline.

Complete data from 91 of the active 95 subjects at 48-month follow-up show that they did not differ significantly from the original study cohort with regard to baseline variables of age, BMI, or AHI (**Table 2**). With regard to secondary patient-based outcomes, 89 subjects had a median FOSQ score of 18.6 (Q1, 16.2; Q3, 19.6), which demonstrates significantly improved sleep-related quality of life, on average, when compared with baseline (17.5 ± 2.9 vs 14.6 ± 3 , $P = .01$). This finding shows that mean levels are significantly improved over baseline, although lower (≤ 17.9) than fully normal values (**Figure 2**). ESS scores (n = 89) at 48 months have a median value of 6 (Q1, 4; Q3, 10) and significantly less daytime sleepiness, on average, when compared with baseline (7.3 ± 4.9 vs 11.4 ± 5.1 , $P = .01$). The average Epworth scores are therefore within the range of normal (≤ 10) and likewise stable over time (**Figure 3**). Snoring improvement was also consistent over time, with 91% of subjects (n = 89) and 85% of bed partners (n = 92) reporting soft or no snoring at 48 months versus only 22% of subjects and 17% of bed partners at baseline (**Figure 4**). A total of 81% of subjects (75 of 93) self-reported nightly use of the device at 48 months, which remained unchanged since 24-month follow-up (**Figure 5**).

Three patients died within the first 36 months from the events described above. These deaths were fully adjudicated

**Figure 3.** Epworth Sleepiness Scale results over time: normal level of daytime sleepiness ≤ 10 . Results in mean and standard deviation.

by a data safety monitoring committee and determined to be unrelated to the implant procedure or device. Throughout 48 months of follow-up, there have been a total of 5 serious adverse events (5 of 126, 4.0%). Three patients underwent elective explantation as described above, and 2 required subsequent surgery between 36 and 48 months to replace malfunctioning device components (1 sensing lead due to insulation breach and 1 stimulation lead and implantable pulse generator to reposition the electrode location to improve therapy response). The revision operations were without complications or significant sequelae. Since the 36-month follow-up, nonserious adverse events continue to decrease (**Table 3**) with fewer cases of discomfort from electrical stimulation or tongue abrasion. There is ongoing intermittent need to adjust stimulation levels to improve function (3 patients) or check the function and reset the parameters of the patient-controlled handheld remote (9 patients).

Discussion

OSA is a prevalent disorder in the adult population that increases the risk of cardiovascular morbidity and motor vehicle accidents.^{1,2} Clinically, OSA patients present with poor sleep quality, loud bothersome snoring, and excessive daytime sleepiness. Upper airway surgery is an option for patients with symptomatic OSA who are unable or unwilling to adhere to CPAP therapy. OSA operations, however, are often only partially effective, are painful, and require prolonged recovery times. The limited effectiveness of sleep surgery may be due to the focus on reducing soft tissue obstruction while failing to address the underlying increase in airway collapsibility caused by reduced neuromuscular tone, which is thought to be the primary pathophysiologic basis for OSA.^{5,6}

The present study is an ongoing multicenter longitudinal observational study of the original STAR trial subjects 48 months after implantation with an UAS device. A previously published study showed that the primary outcome AHI remained low on average (mean, 6.2) at 36 months.¹³ Patient-based outcomes at 36 months demonstrated ongoing

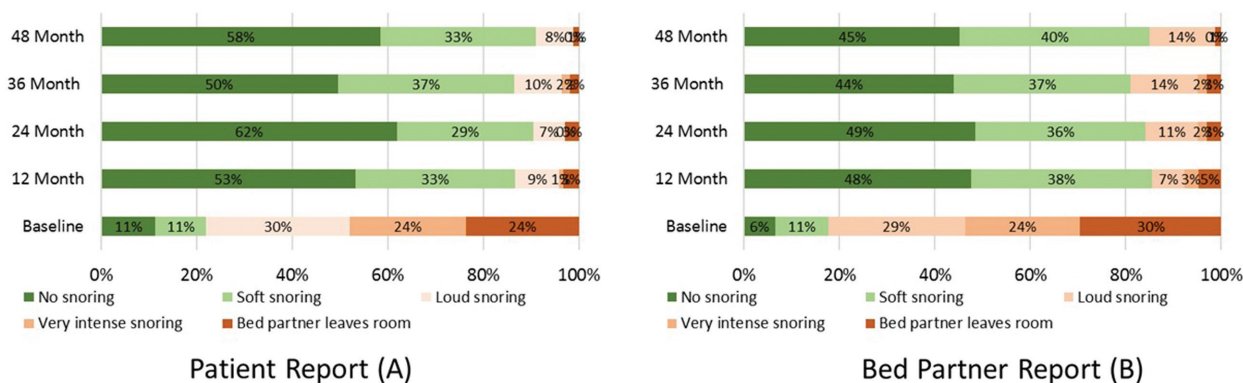


Figure 4. Change in self-reported (A) and bed partner-reported (B) snoring intensity over time.

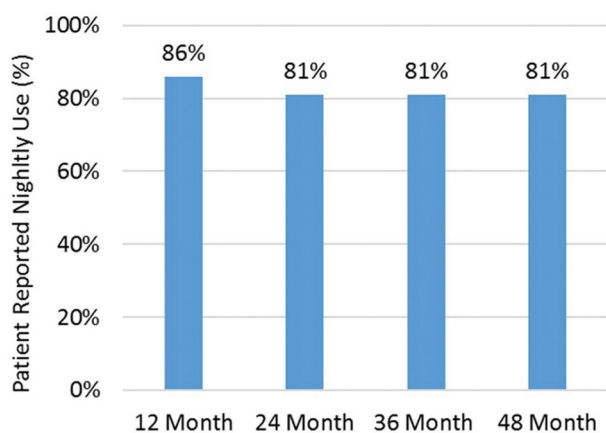


Figure 5. Patient-reported nightly use of upper airway stimulation therapy over time.

improvement of sleep-related quality of life and daytime sleepiness levels on average, as well as low levels of snoring severity. This study confirms the durability of response in these secondary patient-based outcomes at 48 months, which are essentially unchanged from 36-month follow-up. Four years after implantation, patients have symptoms that are significantly improved over baseline, including normal levels of daytime sleepiness, near normal levels of sleep-related quality of life, and improved snoring. Although the present results cannot be confirmed by a 48-month PSG, which was not part of the study protocol, the results suggest ongoing subjective effectiveness of therapy with regard to bothersome symptoms of OSA that are clinically relevant to patients.

Whereas median FOSQ scores show that greater than half of patients have achieved normal levels of sleep-related quality of life, the mean FOSQ scores, though improved over baseline, remain below the normal range, indicating a level of ongoing symptoms among some patients. A recent case report described a STAR trial participant who had ongoing symptoms of snoring and poor sleep despite a significant reduction in AHI from 43 to 12 after implantation of the UAS system.¹⁶ The patient was successfully fitted

with an oral appliance to augment the UAS therapy, with subsequent resolution of symptoms and AHI reduction to 2. This case report highlights that OSA is a chronic disorder that requires ongoing follow-up and adjustment of therapy over time to optimize patient symptoms.

The 48-month data additionally confirms the previously noted high level of therapy adherence, with 81% of subjects self-reporting nightly use of the device. After self-reported nightly use of 86% at 1 year, there was a decrease to 81% at year 2, which has been stable to year 4. These data compare well to CPAP, which is the recognized standard-of-care therapy for moderate to severe OSA. Currently, the Centers of Medicare and Medicaid Services requires documentation of CPAP use—a minimum of >4 hours a night for >70% of nights—to provide coverage for CPAP service. The >4 hours/night is considered minimal, however, as most clinicians stress that patients should wear CPAP all night, if possible. In a prospective trial of CPAP use among >1000 patients, only 40% of patients were adherent to the minimum >4 hours for >70% of nights after 6 months of follow-up.¹⁷ The recently reported SAVE trial (Sleep Apnea Cardiovascular Endpoints) found that patients with a history of moderate to severe OSA and cardiovascular disease randomized to CPAP had no reduction in cardiovascular deaths when compared with non-CPAP controls.¹⁸ One explanation for the negative finding was that the mean duration of CPAP adherence was only 3.3 hours per night in the CPAP group. Although there are potential inaccuracies of self-reported use, it remains notable that 81% of subjects who were previously noncompliant with CPAP now use the UAS system nightly 4 years after implantation. Discrepancy between self-reported CPAP use and objectively measured use by smart card report has been noted, with 60% of CPAP patients reporting nightly use but only 46% meeting criteria for regular use (≥ 4 hours night on >70% of nights).¹⁹ Therefore, it is possible that patients who use a device nightly still fall below recommended standards of use. Although previous evidence suggests that some patients experience modest reductions in systolic and diastolic blood pressure with regular use of UAS therapy, there is currently no evidence to demonstrate a reduction in cardiac events

Table 3. Nonserious Adverse Events over 48 Months of STAR Trial.

Adverse Events	Events, n				Total	Participants with Event, % ^a (n)
	0-12 mo	12-24 mo	24-36 mo	36-48 mo		
Procedure-related nonserious adverse events						
Postoperative discomfort related to incisions	47	1	2	1	51	29.4 (37)
Postoperative discomfort independent of incisions	41	0	1	0	42	27.0 (34)
Temporary tongue weakness	34	0	0	0	34	18.3 (23)
Intubation effects	18	0	0	0	18	11.9 (15)
Headache	8	0	0	0	8	6.3 (8)
Other postoperative symptoms	22	0	0	0	22	11.1 (14)
Mild infection	1	0	0	0	1	0.8 (1)
Device-related nonserious adverse events						
Discomfort due to electrical stimulation	81	23	25	7	136	57.9 (73)
Tongue abrasion	28	12	4	3	47	26.0 (33)
Dry mouth	10	5	2	0	17	12.7 (16)
Mechanical pain associated with presence of the device	7	2	4	0	13	9.5 (12)
Temporary internal device usability or functionality complaint	12	8	1	3	24	15.9 (20)
Temporary external device usability or functionality complaint	11	11	8	9	39	23.8 (30)
Other acute symptoms	21	14	1	2	38	23.1 (30)
Mild infection	1	0	0	0	1	0.8 (1)

Abbreviation: STAR, Stimulation Therapy for Apnea Reduction.

^aPercentage based on original cohort of implanted participants, N = 126.

with UAS therapy.²⁰ Since the STAR trial, modified UAS devices have undergone a software update that allows objective measurement of weekly device usage; however, this update was not available in this cohort of patients.

In addition to the ongoing improvement in patient symptoms, the study found a low rate of long-term side effects and device-related adverse events. Two patients required reoperation between 36 and 48 months for lead-related failure; therefore, ongoing assessment is needed to get a better estimate of the life expectancy of device components. A total of 25 nonserious adverse events were recorded between 36 and 48 months, which was down from 48 reported events between 24 and 36 months and consistent with an observed decreasing trend overall. This decrease is mainly attributable to reduced reports of tongue discomfort with electrical stimulation, which is likely due to therapy acclimation as well as ongoing programming adjustments to improve comfort. It is possible that patients with 48-month follow-up have fewer side effects and complaints than the cohort lost to follow-up.

The main study limitation was the increased number of patients lost to follow-up at 48 months compared with 36 months (25 vs 4). Factors that influence adherence to follow-up include individual patient characteristics, social support, medical staff characteristics, and research study design.²¹ The trend of older age for those who completed follow-up versus those lost at 48 months is consistent with other trials that have noted poorer follow-up in younger cohorts, perhaps due to increased demands of work-life balance among younger subjects.²² With regard to medical

staff, loss of a principal investigator and study site support accounted for 20% of follow-up loss at 48 months. This trial, like many other multiyear trials, is experiencing greater loss of follow-up after 3 years.²³

Conclusions

UAS therapy demonstrates stable, long-term improvement in patient-reported symptoms of sleepiness, sleep-related quality of life, and snoring among patients with moderate to severe OSA who meet selection criteria. The therapy has high rates of adherence as compared with CPAP, with acceptable rates of adverse events. Ongoing follow-up is required to determine the natural product life of the device components.

Author Contributions

M. Boyd Gillespie, date collection, interpretation, and writing; **Ryan J. Soose**, date collection, interpretation, and writing; **B. Tucker Woodson**, data collection, analysis, interpretation and writing; **Kingman P. Strohl**, date collection, interpretation, and revising; **Joachim T. Maurer**, date collection, interpretation, and writing; **Nico de Vries**, date collection, interpretation, and revising; **David L. Steward**, date collection, interpretation, and revising; **Jonathan Z. Baskin**, date collection, interpretation, and revising; **M. Safwan Badr**, date collection, interpretation, and revising; **Ho-sheng Lin**, date collection, interpretation, and revising; **Tapan A. Padhya**, date collection, interpretation, and revising; **Sam Mickelson**, date collection, interpretation, and revising; **W. McDowell Anderson**, date collection, interpretation, and revising; **Olivier M. Vanderveken**, data collection, interpretation, and manuscript revision; **Patrick J. Strollo Jr**, date collection, interpretation, and revising.

Disclosures

Competing interests: M. Boyd Gillespie, Inspire Medical Systems—study investigator, consultant, honoraria; ImThera—study investigator; Medtronic—consultant; Olympus—study investigator; Ryan J. Soose, Inspire Medical Systems—study investigator, consultant; B. Tucker Woodson, Inspire Medical Systems—study investigator, consultant; Medtronic—consultant, royalty; Siesta Medical—royalty; Cryosa—consultant; Kingman P. Strohl, Inspire Medical Systems—study investigator, consultant; Joachim T. Maurer, Inspire Medical Systems—study investigator, consultant, surgical trainer, invited speaker; GlaxoSmithKline, Weinmann, Olympus, ResMed, Neuwirth, Medtronic, and Heinen & Löwenstein, personal fees outside the submitted work; Nyxoah—consultant; ReVent, ImThera—invited speaker; Nico de Vries, Inspire Medical Systems—study investigator, consultant; Philips, Olympus—consultant; Night Balance/ReVent—medical advisor, shareholder, funding from company; Patent—devices, systems, and methods for monitoring sleep position; David L. Steward, Inspire Medical Systems—study investigator, consultant; Jonathan Z. Baskin, Inspire Medical Systems—study investigator; M. Safwan Badr, Inspire Medical Systems—study investigator, consultant; Ho-sheng Lin, Inspire Medical Systems—study investigator, consultant; Intuitive Surgical—consultant; Chechpoint Surgical—consultant; Tapan A. Padhya, Inspire Medical Systems—study investigator, consultant; Sam Mickelson, Inspire Medical Systems—study investigator, consultant; ImThera Medical—research funding; W. McDowell Anderson, Inspire Medical Systems—study investigator; Olivier M. Vanderveken, Inspire Medical—study investigator; SomnoMed—research grant; Nyxoah—research grant, consultant; ReVent—research grant; Philips Electronics BV—consultant; Patrick J. Strollo Jr, Inspire Medical Systems—study investigator, consultant; ResMed—scientific advisory board, research grant; Philips Respironics—research grant; Itamar—consultant.

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