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RECONSIDERATION REQUEST

Hypoglossal Nerve Stimulation for OSA - 0466T, 0467T, 0468T – April 2017 Response to Reconsideration

National Government Services has completed our review of your request to reconsider and revise our local coverage determination (LCD) for Category III CPT® Codes (LCD ID Number L33392) specifically regarding coverage for CPT codes 0466T, 0467T and 0468T.

We appreciate the background on the steps toward FDA approval as outlined in your letter of March 1, 2017. We would, however, emphasize that, as published on Wednesday, August 7, 2013 in the Federal Register, Vol. 78, No. 152, page 48165:

An FDA-regulated product must receive FDA approval or clearance (unless exempt from the FDA premarket review process) for at least one indication to be eligible for consideration of Medicare coverage (except in specific circumstances). However, FDA approval or clearance alone does not entitle that technology to Medicare coverage.

Medicare criteria for reasonable and necessary services are found in CMS Publication 100-08, *Medicare Program Integrity Manual*, Chapter 13 – Local Coverage Determinations, §13.5.1:

Contractors shall describe in the draft LCD the circumstances under which the item or service is reasonable and necessary under 1862(a)(1)(A). Contractors shall consider a service to be reasonable and necessary if the contractor determines that the service is:

- *Safe and effective;*
- *Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary); and*
- *Appropriate, including the duration and frequency that is considered appropriate for the item or service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*

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- *Ordered and furnished by qualified personnel;*
- *One that meets, but does not exceed, the patient's medical need; and*
- *At least as beneficial as an existing and available medically appropriate alternative.*

Obstructive sleep apnea (OSA) is a common chronic medical problem. We applaud your company's efforts to provide additional treatment options for this condition. We agree with you that the goal of treatment of sleep apnea is to "reduce(s) the severity of the co-morbidities, leading to improved health." (Inspire White Paper, page 1)

In considering your technology, we first considered the landscape of sleep apnea severity and the treatments available. As found in the "Clinical Guidelines for the Manual Titration of Positive Airway Pressure in Patients with Obstructive Sleep Apnea. Positive Airway Pressure Titration Task Force of the American Academy of Sleep Medicine. Journal of Clinical Sleep Medicine, Vol. 4, No. 2, 2008,"

OSA severity is defined as RDI/hr:

- Mild = ≥ 5 and < 15
- Moderate = ≥ 15 and ≤ 30
- Severe = ≥ 30

And the goal of the therapy:

4.4.1.1 The CPAP or BPAP selected for patient use following the titration study should reflect control of the patient's obstructive respiration by a low (preferably < 5 per hour) RDI at the selected pressure, a minimum sea level SpO₂ above 90% at the pressure, and with a leak within acceptable parameters at the pressure (Consensus).

We also considered the available (surgical and non-surgical) alternatives and the evidence that any of those achieve meaningful reduction in disease comorbidity and improve health outcomes. In doing so, in addition to your dossier, we reviewed the 2011 AHRQ publication, "Comparative Effectiveness of Diagnosis and Treatment of OSA in Adults AHRQ Pub. No. 11-EHC052-3 July 2011." Some important points from this independent evaluation include that, while there is some data to show severe OSA is a predictor of all-cause mortality, the evidence of benefit of treatment is limited in men > 70 (Medicare population) or women of any age:

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Clinical Bottom Line

Health outcomes of OSA:

- Severe OSA (AHI \geq 30 events/hr) is a predictor of all-cause mortality (HR = 1.5–3.0). ●●●
- One study showed that this correlation was not seen in men >70 years of age or in women.

In addition, this publication rated the quality of evidence showing that surgical treatments of OSA improve health as insufficient or low:

Treatment of OSA [†] :	
<p>CPAP and MAD</p> <ul style="list-style-type: none"> ■ CPAP and MAD are effective treatments for OSA (e.g., they improve sleepiness and lower AHI values). CPAP is superior to MAD in achieving an AHI of \leq5 events/hr. ●●○ □ Studies of MAD predominately exclude patients with comorbidities or unsafe levels of sleepiness. □ Evidence is insufficient to address which patients might benefit most from treatment with CPAP, MAD, or CPAP compared to MAD. ○○○ ■ Types of positive airway pressure machines: <ul style="list-style-type: none"> □ AutoCPAP and fixed CPAP are equally effective. ●●○ □ Evidence is insufficient to compare other CPAP devices (oral CPAP, nasal CPAP, bilevel PAP, flexible bilevel PAP, and humidified CPAP or autoCPAP). ○○○ 	<p>Surgery</p> <ul style="list-style-type: none"> ■ The studies for surgical interventions are limited, and while some studies show efficacy of individual interventions, current evidence is insufficient to determine their relative effectiveness when compared to each other, to sham or no treatment, or to other OSA interventions. ○○○ <p>Other Treatments</p> <ul style="list-style-type: none"> ■ Weight-loss programs may be an effective treatment for OSA (vs. control interventions) in patients who are obese. ●○○ ■ There is insufficient evidence to compare the relative effectiveness of other treatments for OSA, such as implants, exercises, positional approaches, and nasal dilator strips. ○○○ <p>Compliance</p> <ul style="list-style-type: none"> ■ Compliance with OSA treatments: <ul style="list-style-type: none"> □ High AHI and ESS are predictors of improved CPAP compliance. ●●○ □ Evidence is insufficient to evaluate potential predictors of MAD compliance. ○○○
<p>[†]Current research evaluates only intermediate outcomes, and thus these messages may not apply to long-term clinical outcomes.</p>	

Strength of Evidence Scale

- High: ●●● There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.
- Moderate: ●●○ Findings are supported, but further research could change the conclusions.
- Low: ●○○ There are very few studies, or existing studies are flawed.
- Insufficient: ○○○ Research is either unavailable or does not permit estimation of a treatment effect.

This information from the AHRQ publication is important because it reminds us that there are a number of existing surgical and non-surgical treatments for OSA. This is relevant since Medicare coverage is contingent upon an assessment that a new technology “meets, but does not exceed, the patient’s medical need; and” is, “at least as beneficial as an existing and available medically appropriate alternative.”

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With these points in mind, we considered whether Medicare coverage criteria are met for the Inspire device when used to stimulate the Hypoglossal nerve for the treatment of Obstructive Sleep Apnea.

Obviously, the focus of the literature review is the STAR trial and subsequent related publications. I've included some of those here:

- Strollo PJ Jr, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med.* 2014 Jan 9;370(2):139-149.
- Strollo PJ Jr, et al. Upper airway stimulation for obstructive sleep apnea: durability of the treatment effect at 18 months. *Sleep.* 2015;38(10):1593-1598.
- Woodson BT, et al. Randomized controlled withdrawal study of upper airway stimulation on OSA: short- and long-term effect. *Otolaryngol Head Neck Surg.* 2014 Nov;151(5):880-887.
- Woodson BT, et al. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: The STAR trial. *Otolaryngol Head Neck Surg.* 2016; 154(1):181-188.
- Gillespie MB1, et al. Upper airway stimulation for obstructive sleep apnea – patient reported outcomes after 48 months of follow-up. *Otolaryngol Head Neck Surg.* 2017 Feb 1.

We identified many concerns with the STAR trial which are listed below:

- Study supported by device manufacturer
- No concurrent control group
- The included cohort was ill-defined and may not have been optimized with CPAP:
 - “Participants with moderate-to-severe obstructive sleep apnea were eligible for enrollment if they had difficulty accepting or adhering to CPAP treatment.”
- Definition of response left most with moderate OSA:
 - “A response as measured by means of the AHI was defined as a reduction of at least 50% from baseline in the AHI score and an AHI score on the 12-month polysomnography of less than 20 events per hour.”
- Randomized group was not representative of initial cohort and thus not easily reproduced:

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- “At the 12-month visit, the first 46 consecutive participants who met the criterion of having a response to therapy were randomly assigned”
- Few Medicare age participants:
 - Age: 54.5 +/- 10.2 => 15% (n~20 > 65 years)

The clinical outcomes for Strollo (2014) in the main paper centered (appropriately) on the Apnea Hypopnea Index (AHI). The results (briefly) were:

- Mean 12 month AHI = 15.3 +/- 16.1
- Median 12 month AHI = 9

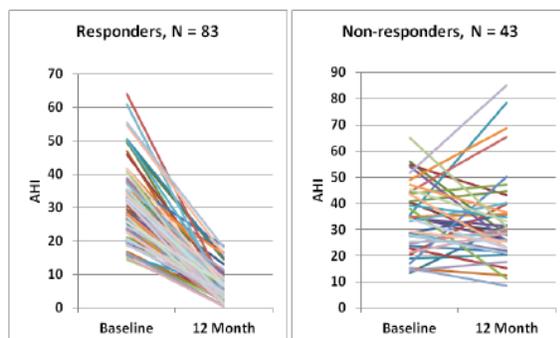
This is important because the outcome means that approximately ½ of the cohort still had mild to moderate OSA!

Even more important, was that:

“Some participants had a significant increase in the AHI score at month 12 (see the Supplementary Appendix). An additional analysis of the association between the baseline characteristics and outcome measures did not identify predictors that differentiated between participants who had a response and those who did not.”

The individual responses were found in the online supplement:

Figure S3. AHI Changes in Responders and Non-responders



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So, not only were the results on average leaving treated subjects with mild-moderate OSA, there were many who were significantly worse in terms of AHI, and the authors were unable to, “identify predictors that differentiated between participants who had a response and those who did not.”

This last observation is particularly important since Inspire has carved out a unique phenotype of individuals who did not have, “complete concentric collapse at the retropalatal airway observed on endoscopy performed during drug-induced sleep.” What is not clear from the publications is the extent to which changes in weight, body mass index, body habitus (e.g. kyphosis), age, upper airway resistance (e.g. nasal congestion or polyps) or other factors could change someone from not having to having this “concentric collapse.” In addition, since 43 subjects who met inclusion criteria did not respond to the Inspire and 19 actually got worse, there are evident limitations in relying on drug-induced sleep endoscopy as a method to determine who is likely to benefit from the Inspire device.

In addition to concerns regarding the clinical outcomes we had concerns with the quality of life (QOL) measures evaluated. While QOL is clearly important, it can be difficult to measure and is highly subject to placebo effect (randomization and appropriate blinding are of utmost importance when considering QOL). There are also often problems with the validity of QOL metrics which makes evaluation even more difficult. This is in fact the case here:

- Strollo (2014) indicated that: “A change of 2.0 or more points in the FOSQ score is considered to indicate a clinically meaningful improvement in daily functioning.”²⁸
 - Citation 28 in Strollo in support of the 2.0 point improvement standard was:
- Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*. 2007;30: 711-719. This citation indicated that:
 - “Functional status, a component of quality of life, was measured using the FOSQ. The FOSQ is a 30-item Likert-style questionnaire with 5 domains that examine the impact of being sleepy or tired on the conduct of daily activities.¹² It has established validity and reliability.”

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- Notably, the statement in Weaver (2007) about established validity and reliability was not supported by a citation. However, citation #12 in the sentence preceding was a reference to another Weaver publication:
- Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20:835-843.
 - Review of Weaver(1997) did not support that a change in the FOSQ of 2.0 points had been prospectively validated as a clinically meaningful improvement.

Others have evaluated QOL metrics for OSA and found the FOSQ lacking. Billings ME, et al. Psychometric performance and responsiveness of the Functional Outcomes of Sleep Questionnaire and Sleep Apnea Quality of Life Index in a randomized trial: the HomePAP study. *Sleep*. 2014;37(12):2017-2024 concluded:

“Neither the FOSQ nor the SAQLI have been extensively validated in randomized control trial settings. Initial FOSQ instrument development used a convenience sample of individuals recruited from a sleep clinic visit to demonstrate test-retest reproducibility and internal reliability.”

We also noted and have reviewed many case reports and case series. We cite a few of those here as a representative sample:

Heiser C, et al. Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience. *Eur Arch Otorhinolaryngol*. 2017 Mar;274(3):1727-1734.

Heiser C, et al. Outcomes of upper airway stimulation for obstructive sleep apnea in a multicenter German postmarket study. *Otolaryngol Head Neck Surg*. 2017 Feb;156(2):378-384.

As you are probably aware, case reports and case series, however numerous, are highly subject to bias in many forms: selection, publication, etc. and are considered a lower quality form of medical evidence.

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In addition to the published and peer-reviewed medical literature, we consider other sources of information which may represent "*accepted standards of medical practice*" such as evidence-based clinical practice guidelines. We realize that Inspire is relatively new and that the process for adding/amending recommendations in evidence-based guidelines may be prolonged. Evidence-based clinical practice guidelines are catalogued by the Agency for Healthcare Research and Quality (AHRQ) in the National Guidelines Clearinghouse (NGC) (<https://www.guideline.gov>). One of the required elements for inclusion in the NGC is that, "3. The clinical practice guideline is based on a systematic review of evidence (...)."

The American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNS/F) has several guidelines recognized by AHRQ and included on the NGC website. AAO-HNS/F also issues documents call Position Statements. Position statements are not evidence based guidelines. The AAO-HNS position statement addressing hypoglossal nerve stimulation for OSA is as follows:

Position Statement: Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnea (OSA)

The American Academy of Otolaryngology-Head and Neck Surgery considers upper airway stimulation (UAS) via the hypoglossal nerve for the treatment of adult obstructive sleep apnea syndrome to be an effective second-line treatment of moderate to severe obstructive sleep apnea in patients who are intolerant or unable to achieve benefit with positive pressure therapy (PAP). Not all adult patients are candidates for UAS therapy and appropriate polysomnographic, age, BMI and objective upper airway evaluation measures are required for proper patient selection.

Submitted for Review 10/2014

Resubmitted for Review 11/30/2015

Resubmitted for Review 1/4/2016

Adopted 3/20/2016

Important Disclaimer Notice (updated 7/31/14)

Position statements are approved by the American Academy of Otolaryngology –Head and Neck Surgery or Foundation (AAO-HNS/F) Boards of Directors and are typically generated from AAO-HNS/F committees. Once approved by the Academy or Foundation Board of Directors, they become official position statements and are added

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to the existing position statement library. In no sense do they represent a standard of care. The applicability of position statements, as guidance for a procedure, must be determined by the responsible physician in light of all the circumstances presented by the individual patient. Adherence to these clinical position statements will not ensure successful treatment in every situation. As with all AAO-HNS/F guidance, this position statement should not be deemed inclusive of all proper treatment decisions or methods of care, nor exclusive of other treatment decisions or methods of care reasonably directed to obtaining the same results. Position statements are not intended to and should not be treated as legal, medical, or business advice.

AAO-HNS position statements include an important disclaimer, “**In no sense do they represent a standard of care.**” In addition, in reviewing the rationale for AAO-HNS/F to develop position statements, the first step in the “Step-by-Step Process for AAO-HNS/F Committees to Take to Develop a New Position Statement” is:

Step 1: Determine the Rationale for the Need for a New Position Statement. Position Statements can be used in advocating with payers regarding coverage policies, issues that members are experiencing with third party payers.

None of the steps in the AAO-HNS/F process include details of a scientific review of the medical literature. Thus, the Position Statement: Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnea (OSA) produced by the AAO-HNS is not a systematic review of evidence, is not included on the NGC website, and does not represent a standard of care.

In summary, while the Inspire hypoglossal nerve stimulation is an additional FDA approved treatment option for individuals with moderate to severe obstructive sleep apnea (OSA) who have been confirmed to fail or cannot tolerate positive airway pressure (PAP) treatments and who do not have a complete concentric collapse at the soft palate level, the available published and peer-reviewed medical literature does not meet Medicare coverage requirements at this time. In particular, there is, in essence, a single prospective clinical trial (STAR) with methodologic concerns and no direct comparison to any of the numerous available alternative treatments. In addition, there are serious concerns as to whether individuals who do not have concentric airway collapse will fail to respond or get worse or that individuals without such collapse will develop it in the future. It is clear that additional published literature is needed and that prospective comparative blinded and randomized trials with clinically meaningful



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outcome measures are required to fully evaluate whether this device meets Medicare coverage requirements.

