The hypoglossal nerve stimulation – current status of evidence and significance for the treatment of obstructive sleep apnea in Germany

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1 Preamble

Obstructive sleep apnea is a common disease that places a burden on affected patients, their families, and society as a whole. For a small number of severely affected patients, the gold standard treatment, a breathing support using positive airway pressure, does not provide a sustainable treatment option. For these patients, hypoglossal nerve stimulation offers an effective treatment option. At the same time, the daily practice in the German healthcare system shows that there is a need for mediation between medical care requirements and reimbursement reality.

Hypoglossal nerve stimulation has been used in numerous countries since the first stimulation system was approved in 2010. In the meantime, the method is in use worldwide (e.g. USA, Germany, Japan, Australia, Switzerland, Netherlands, Great Britain, Sweden, Italy and Spain).

This compilation of literature is based on the current clinical evidence and the current and specific framework conditions of the reimbursement situation in Germany. It originated from the motivation to develop a document with a transparent, systematic approach. It is meant to help all stakeholders involved in care to assess the significance of treatment with hypoglossal nerve stimulation in routine care in Germany.

As a result, this comprehensive work has been compiled, which allows an evidence-based orientation for all decision-makers at different levels and thus an informed discussion among themselves. We would like to thank all those involved in the creation of the document: the company Nyxoah for the contract and funding of this project, the provision of literature and information on the therapy and products, Gerd Gottschalk (GERD Consulting) for the cooperative exchange on the conception of the work and the many technical discussions and revisions, and the entire team of Healthcare Heads GmbH, which supported this project at various points according to the criteria of good scientific practice.

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Disclaimer

The information in this document does not represent any therapy recommendations for the application of hypoglossal nerve stimulation or other methods in individual cases. Information on the use of the products to perform hypoglossal nerve stimulation is provided in the respective instructions for use.

All statements in this document were researched and evaluated with the greatest possible neutrality, based on a transparent, systematic and comprehensible approach in compliance with scientific requirements. All statements made beyond this in the overall context, based on the authors' expertise within the framework of the objective of this document, are substantiated by further references.

The information referring to legal content, such as legal texts and case law, is for information and classification purposes and a basis for the authors' assessment and does not under any circumstances replace legal advice from a lawyer.

With regard to the information on procedure coding and reimbursement, it should be noted that all information was researched and determined using the classifications valid in 2022 and that this information can only apply to this year. In addition, the treatment on site is decisive for the complete and correct coding of individual cases, which can lead to deviating performance identifiers and thus to a different DRG assignment and reimbursement. According to the German Coding Guidelines, the attending physician is responsible for the correct and complete coding of the individual case and the current provisions of the respective valid versions of ICD-10-GM and OPS as well as the aG-DRG-system, including the German Coding Guidelines, always apply.

All information has been researched and presented to the best of our knowledge but does not claim to be correct or complete.

Therefore, the authors do not assume any liability in this context.

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2 Abbreviations

ADHERE	Adherence and Outcome of Upper Airway Stimulation (UAS) for OSA International Registry
AE	Adverse event(s)
AHI	Apnea-hypopnea index
AWMF	Association of scientific medical societies
BDI	Beck Depression Inventory
BfArM	German Federal Institute for Drugs and Medical Devices
BMI	Body mass index
BSG	Federal Social Court
CCC	Complete concentric collapse (of the upper airway at the soft palate)
CEBM	Oxford Centre for Evidence-based Medicine
CGI	Clinical Global Impression of Improvement
CI	Confidence interval
CPAP	Continuous Positive Airway Pressure
cw	Case weight (of a DRG)
DGHNO-KHC	German Society for Otorhinolaryngology, Head and Neck Surgery
DGSM	German Sleep Society and Sleep Medicine
DISE	Drug-Induced Sleep (or Sedation) Endoscopy (Sleep Endoscopy)
DKR	German Coding Guidelines (Deutsche Kodierrichtlinien)
DRG	Diagnosis Related Group
ESS	Epworth Sleepiness Scale
FDA	US Food and Drug Administration
FOSQ	Functional Outcome of Sleep Questionnaire
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
G-DRG-System	German Diagnosis Related Groups System
GKV	Statutory health insurance (Gesetzliche Krankenversicherung)
GPM Study	German Post-Market Study
h	Hour (e.g. in "events/hour")

HGNS	Hypoglossal nerve stimulation (alternative common abbreviation: HNS).
HST	Home sleep testing
ICD-10-GM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification
InEK	German DRG-Institute (Institut für das Entgeltsystem im Krankenhaus GmbH)
IQWiG	Institute for Quality and Efficiency in Healthcare
LOS	Length of stay
MAD	Mandibular advancement device/s
MAUDE	Manufacturer and User Facility Device Experience database
MCID	Minimum clinically important difference
MRI	Magnetic resonance imaging
NRS	Numerical rating scale
NUB	New examination and treatment method (Neue Untersuchungs- und Behandlungsmethode)
ODI	Oxygen desaturation index
OPS	German procedure classification (Operationen- und Prozedurenschlüssel)
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PICOS	Patient/Intervention/Comparison/Outcome/Study type
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient reported outcome
PSQI	Pittsburgh Sleep Quality Index
PSG	Polysomnography
REM	Rapid eye movement
RCT	Randomized controlled trial
SAQLI	Sleep Apnea Quality of Life Index
SGB V	Social Law Book Five

SoC	Standard of Care
STAR	Stimulation Therapy for Apnea Reduction
SAE	Serious adverse event(s)
UAS	Upper airway stimulation
VAS	Visual Analogue Scale
VerfO	Rules of procedure (Verfahrensordnung)
ZE	Supplemental fee

Gender reference

The simultaneous use of different gender-specific designations has been dispensed with to improve legibility. All personal designations apply equally to all genders.

Translation notice

All translations of cited passages from German to English have been done by Healthcare Heads GmbH.

3 Introduction and objective

Obstructive sleep apnea (OSA) is a chronic disease that imposes a significant burden on both the individual patient and society. The successful treatment of obstructive sleep apnea is therefore of correspondingly great relevance. The hypoglossal nerve stimulation (HGNS) therapy represents a treatment option for obstructive sleep apnea.

This document presents the significance of hypoglossal nerve stimulation for the provision of care in the German healthcare system based on scientific evidence. The clinical evidence was researched, evaluated, presented and assessed systematically, transparently and according to defined criteria. The systematic and transparent approach allows a clear understanding of the assessment.

The significance of hypoglossal nerve stimulation in the German healthcare context is presented with the background of the numerous limitations of available therapies. These various therapeutic options are included in the evaluation, in particular the positive airway pressure therapy, which is currently considered the gold standard. The question of reimbursement of the hypoglossal nerve stimulation is essential for the availability in routine clinical practice, which is why it is examined whether hypoglossal nerve stimulation meets the requirements for coverage by the statutory health insurance (Gesetzliche Krankenversicherung – GKV) in Germany as defined in the Social Law Book V (Sozialgesetzbuch SGB V).

The document is explicitly aimed not only at physicians or scientists, but at all professionals involved in the provision of care, including decision-makers of the service providers and payers. In order to create a common basis of information that is comprehensible to all groups and facilitates professional discussion, the medical-scientific content is presented as simply as possible regarding language without reducing the content too much. In addition, basic information on the disease and other relevant aspects are added where this appears helpful for understanding and the overall context.

The structure of this document follows the outlined objective by presenting introductory information on the disease of obstructive sleep apnea, the therapeutic options as well as the reimbursement of hypoglossal nerve stimulation in the in-patient sector. This is followed by a presentation of the systematic literature research and evaluation with the results from 33 publications as a basis for the assessment of the significance of HGNS for care in the German healthcare system. First, the significance of hypoglossal nerve stimulation in the medical context and subsequently the fulfillment of socio-legal requirements are discussed. The conclusion is a summarizing assessment of the method.

4 Summary

The comparatively recent but no longer new method of hypoglossal nerve stimulation (HGNS) is a neurostimulation therapy for the treatment of obstructive sleep apnea (OSA). In this procedure, the hypoglossal nerve is stimulated to trigger contractions of the tongue muscles and thus prevent the upper airway obstruction underlying the disease due to abnormal relaxation of the tongue muscles.

Obstructive sleep apnea is a common chronic disorder that massively impairs patients' sleep as a result of obstructed airflow in the upper airway, leading to numerous symptoms and health risks. Patients are impaired by excessive daytime sleepiness and reduced quality of life, particularly in the more severe courses, and are at increased risk for cardiovascular and other comorbidities (e.g. myocardial infarction, stroke) and even death. Therefore, the disease of obstructive sleep apnea also affects society through significant direct and indirect costs.

With continuous positive airway pressure therapy during the night (CPAP) an effective and safe non-surgical therapy is available, which is considered as first-line therapy according to clinical guidelines. Due to poor adherence to therapy, obstructive sleep apnea cannot be effectively treated with CPAP in approximately half of the cases, leaving a relevant number of patients exposed to the adverse health effects and risks associated with OSA. The therapeutic gap can only be partially closed by the available conservative and conventional surgical treatments due to therapy-specific limitations and risks. Therefore, there is a need for further treatment methods such as the hypoglossal nerve stimulation.

In order to examine the extent to which hypoglossal nerve stimulation can contribute to closing the therapeutic gap while meeting the socio-legal requirements for the reimbursement of services in the in-patient sector in Germany, a systematic literature research and review was performed (see chs. 8 "Systematic literature research and selection", 9 "Systematic literature review" and appendices). Thirty-three publications were identified that were systematically evaluated with regard to relevant parameters for assessing the efficacy and safety of the hypoglossal nerve stimulation method. The assessment was performed across various technologies, as the technical differences of individual neurostimulation systems do not justify different methods.

With two randomized controlled trials, one non-randomized parallel-arm study, eight prospective single-arm treatment studies, three retrospective studies, one case series, three meta-analyses as well as registry evaluations, the assessment of the hypoglossal nerve stimulation method presented here is based on both extensive and high-quality evidence including long-term results up to five years as well as data from clinical routine. The systematic review shows consistent results of long-term effective treatment of obstructive sleep apnea with hypoglossal nerve stimulation with low risks.

The hypoglossal nerve stimulation method is effective and safe and contributes to closing a therapeutic gap, as there are patients with obstructive sleep apnea who are currently not adequately treated. The use of hypoglossal nerve stimulation is also recommended in the S3 guideline of the German Sleep Society (Deutsche Gesellschaft für Schlafforschung und Schlafmedizin, DGSM) for CPAP-intolerance or -inefficacy. The method allows the replacement of more invasive, irreversible, and complex methods with fewer side effects and the optimization of the treatment of obstructive sleep apnea for certain patients. Thus, the method fulfills the socio-legal requirements for reimbursement of services in the in-patient sector since on the basis of the evaluated evidence, the benefit of the method can be considered proven and the requirements for the "potential of a necessary treatment alternative" according to sec. 137c para. 1 SGB V are met, and the method is adequate, expedient, economical and necessary and corresponds to the generally accepted state of medical knowledge. Accordingly, the treatment of obstructive sleep apnea with the aid of hypoglossal nerve stimulation represents a valuable contribution to the improvement of care in Germany for both patients and society.

In conclusion, hypoglossal nerve stimulation as a second-line therapy after CPAP failure can be considered an effective and safe addition to the existing therapeutic options for moderate to severe obstructive sleep apnea. It is already part of the clinical routine not only in Germany and regular reimbursement in the form of a supplemental fee has already been established.

5 Description of the disease

5.1 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing (SDB). According to the International Classification of Sleep Disorders (ICSD-3), OSA is distinguished in adults and children (1). This document refers to the treatment of OSA in adults with hypoglossal nerve stimulation (HGNS) in the German healthcare context.

In Germany, no children are currently treated with HGNS (no treatments were documented in the age group up to under 18 years in 2019, 2020, and January to May 2021 (2)) and the current S3 guideline on OSA, as evidence-based guidance for diagnosis and treatment, only refers to adults (3,4). Therefore, solely OSA in adults is addressed in this document.

OSA is characterized by obstruction of the upper airway during sleep, resulting in cessation of breathing (apnea). Generally, there is a relaxation of the muscles of the upper airway during sleep. In healthy sleep, the upper airway is kept open by a complex interaction of the pharyngeal muscles (including muscles in the area of the tongue and palate). In patients with OSA, however, muscle relaxation leads to blocking (obstruction) of the upper airway. These repetitive obstructions result in apnea or periods of reduced breathing (hypopnea), during which no or less air flows into the lungs, thus impeding gas exchange. This leads to oxygen desaturation (lack of oxygen) in the blood, which has various long-term consequences for the body. An immediate consequence of the breathing disorder is a lack of oxygen in various organs (e.g. brain, heart), which is accompanied, among other things, by the release of stress hormones, which in turn leads to an arousal and interruption of sleep.

This recurring sequence of lack of oxygen and subsequent arousal (sleep fragmentation) causes, among others, the symptom of daytime sleepiness (5), which is considered the most common and important symptom of OSA (6). It leads to patients falling asleep involuntarily, posing a risk factor for accidents, and impairs patients' cognitive performance, social compatibility, and quality of life (4).

OSA is also associated with numerous other diseases (comorbidities) (6). These include cardiovascular diseases, such as high blood pressure, myocardial infarction and stroke, diabetes mellitus type II, and psychiatric disorders (6,7). OSA represents an independent risk factor for comorbidities (4,7,8).

Mortality is increased in patients with OSA (7). This is ascribed to potentially life-threatening comorbidities on the one hand and to OSA itself on the other. The risk of mortality from severe OSA was increased for men younger than 70 years old in a large prospective cohort study of 6,294 participants, and persisted after adjustment for potential confounders (e.g. age, sex, and comorbidity) (9). The mortality risk may increase

up to threefold depending on the severity of OSA (AHI ≥ 30 events/h, severe OSA) compared with no OSA (AHI < 5 events/h) (6).

The occurrence of OSA is determined by several factors, including body mass index (BMI), age, sex, smoking, and alcohol (4).

5.2 Diagnostics of obstructive sleep apnea

A diagnosis is made to enable the initiation of an efficient, adequate and economical therapy for OSA with few side effects (4). The severity, associated disorders and the manifestation of after-effects should be assessed (4). The severity of OSA is assessed by the Apnea-hypopnea index (AHI) in combination with clinical symptoms and comorbid diseases (4). The AHI can be measured either by polygraphy at home or by polysomnography (PSG) as typical during a sleep laboratory visit. It is calculated from the number of apnea and hypopnea events of at least 10 seconds each related to one hour of sleep time and is the main diagnostic finding of OSA (4). OSA is diagnosed when there is either an AHI ≥ 15 events/h of sleep time or an AHI ≥ 5 events/h of sleep time in combination with typical clinical symptoms or relevant comorbidity and the breathing disorder cannot be explained by any other sleep disorder or medical condition or by medications or other substances (1).

OSA is classified into three levels of severity based on the AHI:

- Mild OSA: AHI ≥ 5 events/h
- Moderate OSA: AHI ≥ 15 and < 30 events/h
- Severe OSA: AHI ≥ 30 events/h

The oxygen desaturation index (ODI), sleep time with oxygen saturation below 90%, and various parameters of sleep architecture (e.g. duration of sleep stages) are other relevant parameters to objectify the effects of OSA and non-restorative sleep. Therefore, they are also collected to assess treatment success in clinical studies (see ch. 9).

In addition, questionnaires to assess daytime sleepiness (e.g. Epworth Sleepiness Scale, ESS) as well as performance and vigilance tests are used in the diagnostic process.

The German Federal Joint Committee (G-BA) defined a "step-by-step diagnosis" for the use of various diagnostic instruments in 2004 in annex A of the Guidelines for the Evaluation of Medical Examination and Treatment Methods in Accordance with sec. 135 para. 1 of the Fifth Social Law Book (SGB V) (BUB Guidelines) (10), which will not be discussed in more detail here.

5.3 Importance of obstructive sleep apnea for the patient and the society

From the extensive evidence on OSA, it can be concluded that the disease is of great importance both to the individual patient and to society. The patient himself suffers from numerous and severe impairments of health and daily life, as described in chapter 5.1. The patient's bed partner is also affected, especially by loud snoring (11). The individual's impairments impact society in the form of significant direct and indirect costs from secondary diseases, accidents, workplace absences and the treatment itself (12–14) and thus have a significant health economic relevance. Particularly, the severe forms of OSA are responsible for this. Economic studies show that 65% to 82% of the medical costs are caused by one third of the patients, namely the patients who have the highest cost consumption and are most severely ill (15).

OSA is the most common form of sleep- disordered breathing (5). Men are more likely to be affected by OSA than women and the risk of developing the disease increases with age (4). A systematic review of the literature shows the prevalence of OSA in the German population aged 30 to 69 years to be approximately 26 million (60.1%) affected people (AHI ≥ 5 events/h, all severities of OSA) rather respectively approximately 14 million people (32.9%) affected (AHI ≥ 15 events/h, moderate/severe OSA) (16). In a review of several international studies, the prevalence of OSA (AHI ≥ 5 events/h) is 22% (9% to 37%) for men and 17% (4% to 50%) for women (6).

Severe OSA is less common with at the same time higher morbidity and it has an increased risk of mortality (7). Associated with the symptom of excessive daytime sleepiness, the prevalence for an AHI ≥ 5 events/h (all severities) in international studies is 6% (3% to 18%) for men and 4% (1% to 17%) for women (6).

6 Therapy of obstructive sleep apnea

Successful treatment of OSA can reduce health risks of OSA and its comorbidities (4,7,8). Therefore, several conservative (nonsurgical) therapeutic methods, especially continuous positive airway pressure therapy, as well as various surgical methods, including hypoglossal nerve stimulation (HGNS), are used to treat OSA.

In Germany, the clinical guidelines of the relevant scientific medical societies provide evidence-based recommendations for the application of the various therapeutic procedures. Accordingly, the guidelines represent the "Standard of Care" (SoC), i.e. the generally accepted therapeutic approach based on corresponding evidence. In the following, the relevant guidelines will be presented first before an explanation of the therapeutic methods based on the recommendation in the guidelines.

6.1 Guidelines

For the treatment of OSA, guidelines from two different but cooperating specialties have been identified at the AWMF (Association of Scientific Medical Societies - Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.), the institution responsible for the coordination and publication of guidelines in Germany (cf. ch. 8.5):

- German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC): "HNO-spezifische Therapie der obstruktiven Schlafapnoe bei Erwachsenen" (“ENT-specific therapy of obstructive sleep apnea in adults”) (17).
- German Sleep Society (DGSM): "S3-Leitlinie Nicht erholsamer Schlaf/Schlafstörungen - Kapitel "Schlafbezogene Atemungsstörungen" (“S3-guideline non-restorative sleep/sleep disorders”) – chapter "Schlafbezogene Atmungsstörungen" (“Sleep-disordered breathing”) (4).

A partial update is available for the S3-guideline “nonrestorative sleep/sleep disorders – chapter Sleep-disordered breathing in adults” of the DGSM with the status of July 2020 (3). The update concerns, among others, the chapter "surgical therapy methods", in which HGNS is addressed, as well.

The guideline of the sleep medicine working group of the DGHNO-KHC has not been updated since 09/2015 (more than 5 years) and is therefore considered outdated (17). The revised version is not available at the time of the guideline research for this document (09/23/21, see ch. 8.5). Since numerous new studies have been published in the meantime, recommendations from the outdated guideline must be considered obsolete. In particular, since a more current guideline on the treatment of OSA (3) is available (see above), the recommendation on HGNS from the aforementioned 2015 guideline is not included here.

However, an updated position paper on the treatment of OSA with HGNS from December 2020 is available from DGHNO-KHC (18). This was included as a supplement to the guidelines (18).

6.2 Treatment goal

According to the S3 guideline of the DGSM, the treatment goal for OSA is undisturbed sleep (4). This is defined by an AHI value of less than 15 events per hour of sleep time and the absence of symptoms of daytime sleepiness (4). According to Eastwood et al., treatment of OSA should "prevent airway narrowing and/or collapse in order to maintain optimal breathing during sleep, to reduce comorbidities and to relieve associated symptoms" (19).

6.3 Treatment options

Both surgical and non-surgical therapeutic procedures are available for the treatment of OSA, which can also be used in combination with each other.

6.3.1 Positive airway pressure therapy during the night

The S3 guideline of the DGSM defines CPAP-therapy as the reference method for OSA treatment (4). The acronym CPAP stands for **C**ontinuous **P**ositive **A**irway **P**ressure and is the most common form of positive airway pressure therapy (PAP) (4). CPAP should be used "for moderate and severe OSA (AHI ≥ 15 events/h)" (highest recommendation grade (A), i.e., based on randomized controlled trials) and may be considered for mild OSA (AHI ≥ 5 and ≤ 15 events/h) in association with certain symptoms or comorbidities, e.g. cardiovascular disease or excessive daytime sleepiness (4) (unchanged recommendation in the partial guideline update (3)).

In CPAP, the patient attaches a plastic mask to the head that covers the nose and, if necessary, also the mouth. A tube is connected to the front of the mask connecting it to the ventilator. The ventilator supplies the patient with air at a continuous positive pressure via the connecting tube. This can prevent or reduce collapse and thus obstruction of the upper airway. It is therefore a pneumatic splinting of the upper airway.

CPAP is the most common form of therapy for all severities of OSA and is very effective in improving OSA, its symptoms and comorbidity (when used properly) (4). As a nonsurgical treatment modality, CPAP is comparatively easy to use and has a relatively favorable cost-benefit ratio (20). However, its use is associated with significant challenges in terms of adherence to treatment, which will be discussed in detail in chapter 6.4.

6.3.2 Other conservative therapy methods

Other conservative therapies for the treatment of OSA are also referred to as "non-(C)PAP procedures". They include weight loss, use of mandibular advancement devices (MAD), therapies to increase the muscle tone, positional therapy, and oxygen therapy, each with varying levels of recommendation (3,4). Drug therapy is only available "off label" (without approval) and may be considered in special situations (4).

Mandibular advancement devices (MAD)

MAD is used to widen and stabilize the upper airway by advancing the mandible (4). The treatment with MAD was included in the care of contract physicians by decision of the Federal Joint Committee (G-BA) of November 20th, 2020, and may therefore be provided at the expense of the statutory health insurance if a positive pressure therapy cannot be performed successfully (21). The use of MAD is considered to be especially effective in mild to moderate OSA (11,22) and is particularly recommended for non-obese patients (BMI < 30 kg/m²) and for positional OSA (recommendation grade A) (4).

Positional therapy

Positional therapy aims at avoiding a supine position of the patient and is therefore only useful if the OSA requires treatment exclusively in the supine position (3). It should be considered in patients with mild to moderate positional OSA and only with validated treatment systems (evidence level 1b, recommendation grade B) (3).

Therapy to increase muscle tone

Overall, the available evidence for treatment with muscle tone enhancement to reduce the tendency of the upper airway to collapse is limited, so that only additional use of non-electrical therapies and myofunctional exercises can be considered on a case-by-case basis (recommendation grade B) (4).

Oxygen therapy

Exclusive/sole oxygen therapy is not recommended (4). Supplementary application of oxygen is mentioned as an option in the S3 guideline in case of known hypoxemia in the titration phase of CPAP under careful monitoring of arterial blood gases (4).

Weight loss

Body weight reduction can be considered an overarching therapeutic intervention to be recommended concomitantly to all patients with obesity (recommendation grade A) (4). In addition, bariatric surgery can also be performed (4).

6.3.3 Surgical therapy methods

There are different types of surgical therapeutic procedures. Since HGNS requires the initial implantation of a neurostimulator through a surgical procedure (see ch. 6.5.5.1), it is also listed under surgical therapies. According to the partial update of the DGSM guideline, HGNS should be considered "in patients with CPAP-intolerance or -inefficacy with an AHI 15-65/h and a BMI up to 35 kg/m², and in the absence of anatomic abnormalities and moderate to severe OSA (evidence level 1b, recommendation grade B)" (3). This recommendation is also referred to in the updated position paper of the DGHNO-KHC (18). The method of HGNS is described in detail in chapter 6.5.

"Resection surgery" is intended to remove the obstruction or obstacle to airflow in the upper airway by resecting the underlying structures (e.g. enlarged tonsils (tonsillar hyperplasia)) (3). These include tonsillectomy and uvulopalatopharyngoplasty, which, when used in combination, should be considered for the appropriate cause of OSA (tonsillar hyperplasia) according to the guideline, particularly when other therapy (CPAP, MAD) is not possible or not sufficiently tolerated (evidence level 1a, recommendation grade A) (3). Overall, peri- and postoperative risks as well as possible long-term side effects such as voice changes, taste disorders or difficulties in swallowing should be considered for "resection surgery" (23).

In cases of anatomic particularities and deformities, "facial skeleton displacement therapies" (osteotomies), e.g. maxillo-mandibular advancement, can be used (3). The tracheotomy is considered the last method of choice (3).

In "resection surgery" and "facial skeleton displacement therapies", irreversible changes are created to the patient's anatomy, unlike with HGNS. This means that side effects and undesirable consequences of surgery can lead to lifelong impairment for patients, from which new treatment needs may arise.

If nasal breathing is impaired in addition to OSA, resulting in CPAP-intolerance, surgery to improve nasal breathing should be considered as it may relieve symptoms of OSA and improve acceptance of CPAP-therapy (3).

There are no clear recommendations for other surgical therapeutic procedures in the updated guideline (3,4).

6.4 Limitations of positive airway pressure therapy

Adherence to treatment is the determining factor for the efficacy of CPAP (24). On the one hand, this means that the device and mask must be used correctly, e.g. to avoid leakage. On the other hand, it is necessary that the patient uses the therapy regularly and persistently (24). Studies have shown that the efficacy of CPAP increases with duration of use (24–26). Based on various studies, a threshold for minimum usage of CPAP has been

established at four hours per night on at least five nights per week (or 70% of nights) (11,22,25,26).

The main limitation of CPAP is that if the therapy is not applied correctly or persistently enough, the therapeutic effect fails to develop or the therapy is completely discontinued (non-adherence) (25,26). Although CPAP is seen as the gold standard (22,27), successful treatment of OSA is challenging due to limited adherence (25,26,28).

The use of CPAP is often associated with various side effects, mainly caused by the mask and the positive pressure (25,26). Side effects include that i) the patient has to exhale against the continuous positive pressure, which can lead to a feeling of dyspnea, ii) wearing the mask is perceived as uncomfortable and oppressive, iii) the constant airflow dries out oral and nasal mucosa, iv) the considerable noise caused by the CPAP machine disturbs night's sleep and leads to family and psycho-social strain.

The side effects pose a challenge for the patient (29) and often result in not only insufficient use of CPAP, but also complete discontinuation of the therapy (30). A recent study of 1,484 patients showed a significant correlation of mask-related side effects with non-adherence in long-term therapy (31). The discontinuation rate in the first seven days after CPAP initiation is described in the literature as 5% to 50% according to the guideline (4). In a patient survey, CPAP abandonment s was reported in 60% (263/435) of patients in the first year, in 73% (318/435) within the first three years, and in 86% (375/435) within the first five years of therapy initiation (30).

Moreover, therapy adherence depends on the improvement of daytime sleepiness, performance, quality of life and blood pressure, but also on the patient's environment, education on the disease and therapy as well as other factors (4).

In a treatment history survey, all 929 patients reported previous treatment with CPAP for an average of 3.4 years (standard deviation: ± 3.7); however, nearly half (47%, n = 435) of the patients had discontinued the treatment (30). Insufficient adherence (use less than four hours per night and less than 70% of nights) was reported by 43% of patients (n = 400) (30). Both groups (discontinuation and attempting therapy with insufficient adherence) showed equal results in terms of daytime sleepiness (ESS) and quality of life (FOSQ) (30). The three most frequently reported complaint categories were discomfort because of the mask, side effects related to pressure and the device, and persistent OSA symptoms (30). The authors of this survey call for a differentiated consideration of the reasons for CPAP abandonment in individual cases in order to adjust the further therapeutic procedure accordingly (30).

If CPAP is discontinued as a result of poor adherence or is continued inadequately and thus ineffectively, the health risks caused by OSA (see ch. 5) continue unchanged (32). There is a corresponding need for effective and safe treatment alternatives due to the high non-adherence to CPAP of about 50% (19,33). Whether, how and how successfully patients who do not (sufficiently) use CPAP are treated depends on the individual case.

Alternative treatment options for OSA are needed because of the limitations of other treatment methods (e.g. MAD, positional therapy) in terms of patient selection and efficacy, as well as the balance of benefits and risks associated with "conventional" surgical procedures (32). This applies in particular to severely affected patients, which in turn account for the majority of costs (15). The HGNS could, based on the available evidence (see ch. 9), fill a therapeutic gap here for certain patients.

6.5 Treatment with hypoglossal nerve stimulation

In the following chapters, the mechanism of action and the underlying technology as well as their significance for the method of HGNS are explained first. Furthermore, the application of HGNS from indication to long-term use by the patient and the spread of the method are presented.

The effects and possible side effects of treatment of OSA with HGNS are discussed in detail in the systematic literature review in chapter. 9.2.

6.5.1 Mechanism of action

In obstructive sleep apnea, muscle relaxation in the upper airway leads to complete or partial obstruction, resulting in impaired breathing (see ch. 5.1). The mechanism of action of HGNS is to keep the upper airway open during sleep by contracting specific muscles (especially the genioglossus muscle as part of the tongue muscles) to counteract obstruction. The genioglossus muscle is the most important muscle for dilating the upper airway (11). As a result of muscle contraction, the tongue moves forward (protrusion), widening the airway behind it (34). Muscle contraction is achieved by electrical stimulation of the associated motor nerve, the hypoglossal nerve. The hypoglossal nerve is the twelfth and last of so-called cranial nerves, which are characterized by the fact that they extend directly from the brain into the body. They are considered peripheral nerves, making treatment with HGNS classified as peripheral neurostimulation therapy. Based on its mechanism of action, HGNS is also called a functional surgical or pacemaker-based therapy (5).

Unilateral stimulation of the paired hypoglossal nerve is sufficient to produce the desired effect on muscle tone and to permit unobstructed breathing (35). According to recent studies, there are indications that bilateral stimulation of the hypoglossal nerve leads to improved treatment results, depending on the individual neuroanatomical conditions (36).

A clinical advantage of HGNS is that, unlike in other surgical therapies, improvement is achieved at multiple levels of the upper airway simultaneously with only one procedure (32,36–38). The simultaneous widening of the airway not only at the level of the tongue base (retrolingual), but also at the level of the soft palate (retropalatal) can be explained

by a linkage of the involved muscles ("palatoglossus coupling") (39) and is more pronounced in bilateral than in unilateral protrusion of the tongue (36). According to Dedhia et al, studies show through drug-induced sedation endoscopy or other imaging techniques that HGNS leads to enlargement of the retropalatal and retrolingual space (32). Safiruddin et al. found an enlargement of the retropalatal area by 56.4% and 180.0% (each p = 0.002) and of the retrolingual area by 184.1% (p = 0.006) and 130.1% (p = 0.008) with therapeutic stimulation during awake and drug-induced sedation endoscopy, respectively, (38).

Successful stabilization or activation of the upper airway muscles, particularly the genioglossus muscle, as a result of HGNS eliminates or improves the obstruction that causes reduced breathing in the form of apnea and hypopnea events. The underlying abnormal muscle relaxation is related to neuromuscular dysfunction and a defective negative pressure reflex of the genioglossus muscle to negative pressure in the upper airway (32). Accordingly, the point of action of HGNS is directly at the site of the underlying dysfunction. This connection may explain why HGNS is a very effective therapeutic option in many cases.

6.5.2 Underlying technology

6.5.2.1 Development history

In 1996, a first study on the successful application of HGNS in humans (still without implanted stimulator) was published (40). Only after more than a decade of further development of this method, the first study with a commercially implantable HGNS system was published in 2011 (41). Different technologies for performing HGNS were developed at the same time and in the following years. The associated initial publications followed in 2012 (42), 2013 (43) and 2020 (19).

Numerous studies (including two randomized controlled trials (RCTs)) have been conducted worldwide since the introduction of implantable HGNS systems 10 years ago demonstrating the efficacy and safety of the method. 33 publications were included in the systematic literature review alone that met the specific inclusion criteria for the review (see ch. 8). With increasing use of the method over the last 10 years, the technology as well as patient selection, implantation technique and postoperative treatment have been further developed and improved (5).

The different technologies all pursue the same goal of preventing the obstruction of the upper airway resulting from muscle relaxation by activating or stabilizing the muscles (contraction). They differ in the technical implementation as well as the details of the type of stimulation. From the perspective of the application of HGNS, the following differences appear relevant according to the regulations and requirements in the German healthcare system:

- unilateral/bilateral stimulation
- respiration-dependent/-independent stimulation
- Energy source implanted/external
- One-piece/multi-part device design.

Essential components of all technologies are an energy source, an implantable pulse generator and the stimulation electrodes as well as a software for programming the stimulation parameters. The energy source feeds the impulse generator which delivers an electrical impulse set by the software through the stimulation electrodes to the hypoglossal nerve, resulting in muscle activation.

In unilateral, respiration-dependent stimulation, the impulse occurs on the medial branch of the hypoglossal nerve during the inspiratory phase (44). A pressure sensor located in the chest wall controls the stimulation so that it occurs only during inspiration (42).

In contrast, unilateral continuous stimulation is applied to the proximal part of the hypoglossal nerve (main trunk) (43). The nerve fibers of the hypoglossal nerve can be activated by witching the six electrodes against each other in different ways with regular recovery pauses due to the constant rotation of the electric field (43).

Bilateral stimulation is performed with a cyclic stimulation rhythm at the distal hypoglossal nerve branches (11). Phases with several short stimulation pulses alternate in a regular rhythm with rest phases without stimulation (45) (so-called "duty cycle").

Since the energy source for generating the stimulation pulse has a limited lifetime, its technical realization is particularly relevant for patients. Once when the energy source is used up, it must be replaced in another surgery in order to continue the HGNS therapy. There are currently three different technologies for the energy supply that are also related to the device design.

In the two unilateral stimulation technologies, the energy source and impulse generator are in the same device unit and fully implanted in the patient. The unilateral, respiration-controlled stimulation technology receives energy from a battery with a life span of typically 11 years (46). The energy source for unilateral continuous stimulation is rechargeable via an external charger and has a life span of tento 15 years (34).

In the case of bilateral cyclic stimulation, the energy source is located outside the body in a so-called activation chip and is attached to the skin over the implanted neurostimulator with a special patch for nocturnal stimulation (45). The energy is transmitted by induction and the stimulation can only take place when the patient switches the energy transmission on. This technology has been further developed so that both the stimulation electrodes and the impulse generator are located in the same device unit. The small, saddle-shaped implant consists of a so-called "antenna (saddle)" and two "legs", each with

two metal plates (electrodes), via which the stimulation impulse is delivered to the hypoglossal nerve (45).

6.5.2.2 Currently available products

Three products are currently available in Germany for the treatment of OSA with HGNS:

1. Genio (Nyxoah S.A., Mont-Saint-Guibert, Belgium)
   Bilateral cyclic stimulation technology
2. Inspire (Inspire Medical Systems, Inc., Golden Valley, MN, USA),
   Unilateral, breath-controlled, stimulation technology.
3. aura6000 (LivaNova PLC, London, UK, formerly ImThera Medical, Inc.)
   Unilateral continuous stimulation technology.

Another product, the Apnex Medical system (HGNS, Apnex Medical Inc., St. Paul, MN, USA) for unilateral breath-controlled stimulation was initially used successfully (41,47). The system is no longer available because business activities were discontinued by the company in 2013 (34).

6.5.3 Cross-technology assessment

In the past, there were different opinions on whether the neurostimulation system used in each case with its specific characteristics has an influence on the definition of the method of HGNS. In this context, the G-BA has passed a resolution on the question of whether HGNS using a "partially implantable stimulation system" falls under the regulation pursuant to sec. 137h para. 1 SGB V (new examination and treatment methods using high-risk medical devices) (48). The designation "partially implantable" can be explained by the fact that the energy supply is not implanted with the technology in question for bilateral, cyclic stimulation – unlike with the other technologies. The actual stimulation system with the stimulation electronics responsible for the activation impulse is also fully implanted in this system.

In the "Supporting Reasons" for its decision of March 5, 2020, the G-BA determined, in accordance with ch. 2, sec. 38, para. 2, clause 1 of the rules of procedure, that for electrostimulation of the hypoglossal nerve by a "partially implantable stimulation system", there is no significant difference to fully implantable stimulation systems

- neither with regard to the principle of action,
- nor to the field of application (49).

According to the G-BA, the external energy supply has no influence on the justification of the therapeutic effect, which is the opening of the upper airway by lifting the tongue muscle (49). In summary, in the opinion of the G-BA, the treatment of OSA with the "partially implantable stimulation system" does not represent a new theoretical-scientific

concept (49). Accordingly, the application of the requested stimulation system does not lead to the fact that "(...) a transfer of the available findings on the benefit including any risks of the already introduced systematic approach [application of other systems, authors' note] (...) would not be justifiable from a medical-scientific point of view (49).

According to the G-BA's reasoning, all currently available stimulation technologies are "based on the same theoretical-scientific rationale" because they all result in "electrical stimulation of the hypoglossal nerve by means of electrodes implanted in close proximity" "with the aim of causing contraction and elevation of the tongue muscle" (49). Furthermore, the explanations of the G-BA state that, under the mentioned conditions, the "available findings on the benefits including any risks" that have been collected with the different technologies are transferable.

This assessment by the G-BA is also reflected in the uniform OPS-coding and reimbursement (see ch. 7). The German Federal Institute for Drugs and Medical Devices (BfArM), which is responsible for the maintenance and further development of the German procedure classification OPS (“Operationen- und Prozedurenschlüssel”), has on request confirmed that the existing OPS-code for the implantation or exchange of a system for peripheral neurostimulation with electrode implantation or exchange: system for hypoglossal nerve stimulation 5-059.c7 “Implantation oder Wechsel eines Neurostimulators zur Stimulation des peripheren Nervensystems mit Implantation oder Wechsel einer Neurostimulationselektrode: System zur Hypoglossusnerv-Stimulation“ is to be used for the implantation of the system for bilateral, cyclic stimulation, which perhaps differs most from the other technologies in its technical design (written information from BfArM, provided by Nyxoah S.A.). Accordingly, reimbursement for in-patient implantation of the stimulator is also covered uniformly by the supplemental fee defined by OPS-code 5-059.c7 (ZE2022-187) (50).

Consistent with the decision of the G-BA and the uniform OPS-coding and reimbursement, the guideline recommendation is to use the "method HGNS" without differentiation of specific stimulation systems and types with the evidence transparently presented separately according to studies with the different technologies (3).

In contrast, the updated position paper on HGNS by the DGHNO-KHC (18) highlights differences between the three stimulation systems which do not appear to be justified against the background of the G-BA decision, at least not to the described extent. As per the above mentioned statements of the G-BA (49), the "available findings on the benefits including any risks" are transferable between the currently available technologies for HGNS due to the comparable theoretical-scientific concept and field of application, despite the depicted differences in the details of the technical design and application,.

Therefore, the evidence for the method of HGNS was researched and evaluated across technologies in this document (see chs. 8 and 9) following the reasoning of the G-BA as the highest body of the self-government in the German health care system.

6.5.4 Indication and requirements for treatment

Accurate patient evaluation is critical for good treatment response in HGNS (18). Several criteria must be examined and considered during the indication process for HGNS to be used successfully for the treatment of OSA in individual cases (3,37). These include in particular:

- CPAP-intolerance or -inefficacy (3)
  Since HGNS is approved and used as a second-line therapy, the requirement is that CPAP cannot be used successfully.
- Moderate to severe OSA (AHI of 15 to 65 events/h) (3)
  The severity of OSA and the specific AHI should be determined in advance using appropriate diagnostic methods (e.g. PSG). The initial limitation of use to an AHI of up to 50 events/h does not seem justified based on further study results (18).
- Overweight up to a BMI of 35 kg/m² (3)
  The threshold value for BMI was raised from an initial 32 kg/m² to 35 kg/m² based on positive results from further studies (18).
- Absence of anatomic abnormalities (3)
  In case of anatomic abnormalities (e.g. mandibular retrognathia (backward position of the mandible in relation to the anterior skull base), the efficacy of HGNS is limited and other surgical therapies (e.g. maxillo-mandibular advancement) may be considered.

The S3 guideline of the DGSM recommends considering HGNS if the mentioned criteria are present (recommendation grade B) (3). This recommendation is based on evidence level 1b (as determined by a systematic literature research until 04/30/2019), according to which, among other things, results from a randomized controlled trial were included (3). The indication criteria defined in the German guidelines are based on the available international evidence and therefore also reflect the approach in other countries.

The indication still requires a detailed medical sleep examination with determination of relevant baseline parameters such as AHI, ODI and sleep architecture. In addition, the literature is unanimous in calling for the patient's appropriate motivation for treatment, including long-term adherence, if necessary with repeated adjustments of the stimulation parameters (5,18,37) (titration, see ch. 6.5.5.3).

6.5.4.1 Indication criterion "CPAP-intolerance or -inefficacy"

As second-line therapy, if HGNS is used, treatment with CPAP must have been proven unsuccessful previously. There are many reasons for unsuccessful CPAP (see ch. 6.4). However, for comparability of treatment quality and success, it is a prerequisite that patients are selected uniformly based on the indication criteria. This also requires a uniform application of the indication criterion "CPAP-intolerance or -inefficacy". Since the

definition of the criterion cannot be completely based on concrete measured values, the corresponding specifications are all the more important.

There is no definition of "CPAP-intolerance or -inefficacy" in the DGSM S3 guideline. The literature recommends the use of CPAP for at least 4 hours per night for at least 5 nights per week (22). Mashaqi et al. define PAP failure as a persistent increase in AHI to at least 15 events/h and intolerance as “the inability to use PAP therapy continuously (more than or equal to five nights per week for more than or equal to four hours every night) or the unwillingness to use PAP therapy again after quitting in the past” (11).

In its updated position paper, the sleep medicine working group of the DGHNO-KHC demands that the reasons for non-adherence to CPAP be explained and that the presence of contraindications be documented (18). While contraindications can be documented rather objectively on the basis of medical findings, this is less possible for the criteria of non-adherence or intolerance, so that the precise and complete documentation for the traceability by third parties is certainly of particular importance. Fietze et al. propose a definition of the five terms: "PAP-inacceptance", "PAP-incompatibility", "PAP-intolerance", "PAP-failure" and "PAP-discontinuation" in their review (51). For example, "PAP-intolerance" is defined as "an objectively proven average use of less than 4h over an extended period of time despite reasonable attempts to optimize therapy" (51).

6.5.4.2 Meaning of Complete Concentric Collapse

When the upper airway musculature relaxes in the setting of OSA and collapses into the airway lumen causing obstruction, different patterns of this muscle collapse result depending on the degree of involvement of different muscle groups. For the indication of HGNS, a specific collapse pattern, Complete Concentric Collapse of the upper airway at the soft palate (CCC), is of particular importance because CCC is associated with a lack of efficacy in the unilateral, breath-controlled stimulation technology (37,42,52,53).

A so-called drug-induced sleep (or sedation) endoscopy (DISE) is performed as part of the indication to identify and exclude such patients prior to treatment. This examination simulates the relaxation of the airway muscles during sleep and allows a more precise assessment of the degree and extent of the collapse (11). For drug-induced sleep endoscopy, the patient is sedated to sleep while the upper airway can be viewed through an endoscope to assess the collapse pattern according to standardized criteria regarding anatomical level, direction and degree of collapse (53). In a systematic study of the collapse pattern using drug-induced sleep endoscopy, the proportion of patients with OSA who had CCC was 37.3% (158 of 424 patients) (54).

In accordance with the available evidence, the consensus among international and national recommendations is that unilateral breath-controlled stimulation should not be used if CCC is diagnosed (3,11,18,37).

According to the partial update of the S3 guideline of the DGSM, bilateral cyclic stimulation should also not be used in patients with CCC (3). In this update published in 2020, the chapter on surgical therapy methods was revised, too. However, recent study results showing comparable efficacy and safety with and without CCC for bilateral cyclic stimulation (55) have not been included, yet. Based on these study results, CE-marking for use with CCC was granted in October 2021 for the medical device in question (Genio System, Nyxoah S.A., Mont-Saint-Guibert, Belgium) (55). In the USA, the Food and Drug Administration (FDA) has allowed accelerated approval for use in patients with a CCC with "Breakthrough Device Designation" status (56). This means that it will no longer be necessary to rule out CCC as part of the indication by means of a drug-induced sleep endoscopy for the application of bilateral cyclic stimulation with the Genio system in the future (55).

The unilateral, continuous form of stimulation can also be used in patients with CCC (3,18).

6.5.4.3 Contraindications

Other forms of sleep-disordered breathing should be carefully excluded as they have other causes and are not indications for HGNS. These include central sleep apnea and sleep-related hypoventilation or hypoxemia (11). For example, it should be ensured that the proportion of central apneas in the total AHI does not exceed 25% before treatment with HGNS(11,18). Neuromuscular diseases (18) or pregnancy (11) need to be ruled out, too. In addition, device-specific contraindications must be observed, such as hypersensitivity to materials of the system components and general contraindications like contraindications to surgery under general anesthesia.

6.5.5 Treatment process

Treatment with HGNS is divided into three main stages, which are described below:

1. Implantation of the neurostimulator
2. Activation of the hypoglossal nerve stimulation
3. Application of hypoglossal nerve stimulation.

6.5.5.1 Implantation of the neurostimulator

The neurostimulator is implanted in a surgical procedure under general anesthesia. Depending on the technology and the experience of the surgeon, different surgical steps are required resulting in a surgery time of between approximately one and three hours.

In the unilateral stimulation technology, the hypoglossal nerve is exposed via an incision in the neck below the chin and a cuffed electrode is placed around the nerve at an appropriate location (42,43). The impulse generator and the energy source are implanted

via another incision in a subcutaneous pocket on the upper chest (42,43). The electrode and the impulse generator are connected by a subcutaneously tunneled lead wire (42,43).

For unilateral, breath-controlled stimulation, a third incision is required to implant an additional pressure sensor on the chest in the intercostal muscles. A lead wire connects the impulse generator with the pressure sensor through a subcutaneous tunnel (42). According to the manufacturer's current instructions for use, the pressure sensor can also be inserted through the incision for the pulse generator in certain patients whereby a third incision can be avoided ("two incision approach") (57).

The miniaturized neurostimulator for bilateral cyclic stimulation technology, which includes both the pulse generator and the electrodes, is implanted only through an incision below the chin. After exposure of the hypoglossal nerve, the electrodes are placed and fixed at an appropriate location on the hypoglossal nerve.

In all technologies, the opening of the upper airway is controlled with a nasal endoscope during the procedure. Intraoperative neuromonitoring is used to identify and monitor the hypoglossal nerve. The correct positioning and functionality of the neurostimulation system are already tested intraoperatively using special equipment.

The typical length of stay (LOS) in hospital is three to four days based on the experience to date in Germany.

6.5.5.2 Activation of the hypoglossal nerve stimulation

After the stimulation system is implanted, stimulation can be activated after approximately four to six weeks of healing time (11). The patient-specific adjustment of the different stimulation parameters to optimize therapy is called titration. Titration takes place in a multistage process while the patient is either awake or asleep (5). In the awake state, the threshold values for triggering an initial muscle/tongue movement as well as discomfort or pain can be determined and titration during sleep is used to fine-tune the stimulation parameters (5,45). The latter takes place (similar to the adjustment of CPAP) under the direct monitoring of the relevant sleep- and respiration-related parameters and of the air flow through the upper airway by the means of a polysomnography (32) and is usually performed in a sleep laboratory in Germany (5).

The muscle activation can be individually adjusted by regulating the stimulation frequency as well as amplitude and duration of the electrical impulse. The parameters are adjusted in such a way that the patient receives the greatest possible benefit from the therapy without causing discomfort or undesirable arousals. Further parameters, e.g. the delay time until the start of stimulation (45) or the sensing algorithm for breath-controlled stimulation (42) can be adapted individually. In addition, the neurostimulator stores information on usage which can be read out by the attending physician and enables an objective assessment of therapy adherence.

6.5.5.3 Application of hypoglossal nerve stimulation

With the neurostimulation system implanted and set, the patient can perform HGNS treatment independently and permanently at home. The patient activates or deactivates the stimulation as needed using a remote control. In the case of bilateral cyclic stimulation technology, it is necessary to fix the external energy source on the skin over the implanted neurostimulator. The HGNS should be used regularly and continuously during night's sleep to achieve the desired therapeutic effect.

Titration, i.e., the adjustment of stimulation parameters, can be repeated at any time to accommodate changed conditions, if necessary (5), which is particularly relevant in chronic diseases such as OSA (32). In addition, the neurostimulation system can be removed and a new one re-implanted, if required (58–60).

6.5.6 Dissemination of the method

The usage of HGNS is presented, on one hand, by concrete data on the frequency of use in Germany, and on the other hand, by the approval status in Germany and other countries.

6.5.6.1 Application of hypoglossal nerve stimulation in Germany

The usage of HGNS in Germany can be determined with the help of the "DRG-statistics" of the Federal Statistical Office of Germany (Destatis). Here, the in-patient services provided and coded with OPS-codes in hospital during one year are documented. Implantation or change of a neurostimulator for HGNS can be identified by a specific OPS-code (5-059.c7 "Implantation oder Wechsel eines Neurostimulators zur Stimulation des peripheren Nervensystems mit Implantation oder Wechsel einer Neurostimulationselektrode", see ch. 7.1). Correspondingly, the number of OPS-codes in the DRG-statistics reflects the number of treated cases, subject to any inaccuracies in the documentation process. In 2020, the OPS-code for neurostimulator implantation (5-059.c7) was documented 282 times as reported by the DRG-statistics (61). Table 6-1 provides an overview of the number of OPS-codes in the DRG-statistics since the introduction of specific coding in 2014.

Treatment with HGNS is carried out in about 35 priority clinics in Germany as per the position paper of the sleep medicine working group of the DGHNO-KHC (18).

Table 6-1: Number of OPS-codes for implantation of a neurostimulator for HGNS 2014 to 2020 (61–67).

Year	2020	2019	2018	2017	2016	2015	2014
Number of OPS-code 5-059.c7	282	234	173	145	105	60	38

6.5.6.2 Regulatory approval status in Germany and other countries

Of the currently available stimulation systems, the first to receive CE-marking and thus EU-wide approval was the Inspire System (Inspire Medical Systems, Inc., Golden Valley, MN, USA) in October 2010, followed by approval from the US Food and Drug Administration (FDA) in April 2014 and from the Japanese regulatory agency PMDA in June 2018 (18).

The aura6000 system (LivaNova PLC, London, UK, formerly ImThera Medical, Inc.) received the CE-mark in March 2012 and an FDA pivotal trial for approval in the USA is currently underway (18).

The "youngest" system is the Genio system (Nyxoah S.A., Mont-Saint-Guibert, Belgium) with CE-marking in March 2019 (18,45). An FDA pivotal trial ("DREAM" study) is currently underway at 22 centers for approval in the USA (18). The Genio System has also received CE-mark extension for use in patients with Complete Concentric Collapse (CCC) of the upper airway (which was previously a contraindication) in October 2021 (55) and was granted “Breakthrough Device Designation” status by the FDA in September 2021 (56), allowing for an abbreviated approval pathway in the US.

Neurostimulation systems for HGNS are classified as Active Implantable Medical Devices (AIMDs) by the Medical Device Regulation (MDR (EU) 2017/745) and thus belong to risk class III (class III).

7 Coding and Reimbursement in the hospital

Implantation of the neurostimulator for the treatment of OSA with the HGNS is performed as an in-patient surgical procedure under general anesthesia. Therefore, the service is reimbursed via the aG-DRG-system. The in-patient reimbursement is presented in general terms below. Long-term patient care takes place in the out-patient setting. Since reimbursement in the out-patient sector in Germany varies greatly due to the underlying reimbursement system and because it depends greatly on the individual case, a reliable "standard" cannot be presented. Thus out-patient reimbursement will not be explained here.

All in-patient treatment cases in Germany are billed to the health insurances as Diagnosis Related Groups (DRGs) via the aG-DRG-system. It is irrelevant whether the patients are covered by statutory or private health insurance and in which ownership (e.g. church or private) the hospital belongs. Each individual treatment case is assigned to exactly one DRG. The lump-sum payment for a case can be determined by multiplying the so-called case weight (cw) of a DRG by the base rate.

DRGs are case groups defined by so-called performance identifiers. The performance identifiers include, for example, diagnosis or procedure codes, age, sex and numerous other characteristics. The coding of diagnoses and procedures of a treatment case with diagnosis codes (ICD-10-GM) and procedure codes (OPS) as well as the documentation of all other performance identifiers is the basic prerequisite for a case to be assigned to a DRG. To achieve identical reimbursement for identical services in different hospitals, they must be assigned to identical DRGs. To ensure this outcome, it is necessary to code the services identically. Therefore, rules for correct coding of diagnosis and procedure codes have been introduced. These can be found in the respective valid versions of ICD-10-GM (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification) and the German procedure classification OPS (Operationen- und Prozedurenschlüssel) as well as the German Coding Guidelines (Deutsche Kodierrichtlinien, DKR).

The correct and complete coding of an in-patient treatment case is therefore the basis for the appropriate reimbursement of the case and the hospital's charge settlement with the health insurances.

7.1 Coding for implantation of the neurostimulator for hypoglossal nerve stimulation

The procedures (diagnostic, therapeutic and nursing) as well as the principal diagnosis and, if applicable, secondary diagnoses of a case are to be coded as specifically as

possible. Procedures are coded using OPS-codes while diagnoses are coded as ICD-codes from the currently valid version of the OPS or ICD-10-GM.

7.1.1 ICD-coding of obstructive sleep apnea

Hypoglossal nerve stimulation (HGNS) therapy is used to treat the condition of obstructive sleep apnea (OSA) (see ch. 6.5). Thus, the diagnosis of OSA should be coded with an appropriate ICD-code. For the coding of sleep disorders, the ICD-10-GM provides section G47.- "Schlafstörungen", of which subsection G47.3- "Schlafapnoe" applies to sleep apnea (68). OSA is coded with the ICD-code G47.31 "Obstruktives Schlafapnoe-Syndrom".

7.1.2 OPS coding of the implantation procedure

Various code ranges are available in the OPS for the coding of neurostimulation therapy, defined by different criteria (69). Three categories of OPS-codes are distinguished based on the site of action of the stimulation – on the peripheral or central nervous system or on the spinal cord. The hypoglossal nerve is a cranial nerve and belongs to the peripheral nervous system. Therefore, the appropriate OPS-code for implantation of the system for HGNS can be found in the OPS-code section for other operations on nerves and ganglia 5-059.- “Andere Operationen an Nerven und Ganglien“.

For the correct selection of the OPS-code, a distinction must be made as to whether the stimulation electrodes are implanted at the same time as the neurostimulator. This is usually the case when a system for HGNS is implanted for the first time.

The OPS-code for initial implantation or exchange of a neurostimulator plus electrodes for hypoglossal nerve stimulation is:

- 5-059.c7 „Andere Operationen an Nerven und Ganglien: Implantation oder Wechsel eines Neurostimulators zur Stimulation des peripheren Nervensystems mit Implantation oder Wechsel einer Neurostimulationselektrode: System zur Hypoglossusnerv-Stimulation“.

Based on the instructions for OPS-code range 5-059.c-, which are to be observed in the sense of a coding rule, the implantation of the stimulation electrode is to be coded separately with an OPS-code from 5-059.8 ff. This note is relevant for HGNS technologies in which the electrodes are implanted separately and connected intraoperatively to the stimulator. The OPS-code 5-059.86 “Implantation oder Wechsel von Neurostimulationselektroden zur Stimulation des peripheren Nervensystems: Implantation oder Wechsel einer Elektrode für ein System zur Hypoglossusnerv-Stimulation” is coded additionally for a separate electrode implantation.

The initial setup or reprogramming of the implanted system must be documented using OPS-codes 8-631.30 or 8-631.31 according to the instructions for OPS-code 5-059.c7.

Furthermore, depending on the used technology, more OPS-codes must be used:

- For the implantation of an intercostal sensing electrode for breath-controlled stimulation OPS-code 5-059.h3 „Verwendung eines Neurostimulators zur Stimulation des peripheren Nervensystems mit zusätzlicher Mess- und/oder Stimulationsfunktion: Mit Positionierung eines interkostalen Drucksensors zur Detektion des Atemsignals“ is used.
- If the used technology is suitable for a whole-body MRI (e.g. bilateral stimulation) this is coded with OPS-code 5-934.3 „Verwendung von MRT-fähigem Material: Neurostimulator, Ganzkörper-MRT-fähig“.
- For the use of electrodes suitable for a whole-body MRI, OPS-code 5-934.4 „Verwendung von MRT-fähigem Material: Eine oder mehrere permanente Elektroden zur Neurostimulation, Ganzkörper-MRT-fähig“, applies.

If only a neurostimulator is implanted without a separate implantation of stimulation electrodes (e.g. to replace the implanted energy source), OPS-code 5-059.d7 „Wechsel eines Neurostimulators zur Stimulation des peripheren Nervensystems ohne Wechsel einer Neurostimulationselektrode: System zur Hypoglossusnerv-Stimulation“ is applicable.

Additional OPS-codes are available for revision (5-059.1) and removal (5-059.2) of the neurostimulator.

In summary, the initial implantation of a system for HGNS is coded with the specific OPS-code 5-059.c7. Depending on the applied technology in the individual case, other OPS-codes may also have to be specified for documenting services of the corresponding treatment case without changing the DRG assignment and thus the reimbursement (see following chapter). If technology-independent services are performed and coded during the in-patient stay, these can lead to a change in the DRG assignment and thus the reimbursement.

7.2 Reimbursement in the aG-DRG-system 2022

Based on the individually applicable performance identifiers on site, in particular the diagnosis and procedure codes, the corresponding treatment case is assigned to a DRG. Typical cases coded as presented in the previous chapter will be assigned to DRG 802C “Andere nicht ausgedehnte OR-Prozedur ohne Bezug zur Hauptdiagnose ohne mäßig komplexe OR-Prozedur” in 2022.

Reimbursement of treatment cases via DRG 802C alone is not appropriate. Therefore, the additional costs are reimbursed by a supplemental fee. The OPS-codes 5-059.c7 and 5-059.d7 trigger the supplemental fee ZE2022-187[1] of undefined amount (50).

Accordingly, the in-patient reimbursement for the implantation of a neurostimulator for treatment with HGNS consists of three components.

- DRG tariff: approx. € 5,976[2]

  Coding the diagnosis code G47.31 for OSA in combination with the OPS-code for neurostimulator implantation/change 5-059.c7 or neurostimulator change without electrode change 5-059.d7 and, if applicable, any additional codes (e.g. for electrode implantation, intercostal sensing electrode implantation for breath-controlled stimulation, and/or use of MRI-enabled material) will result in DRG 802C in 2022.

- Undefined supplemental fee for neurostimulators for hypoglossal nerve stimulation ZE2022-187 „Neurostimulatoren zur Hypoglossusnerv-Stimulation“.

  For the implantation of neurostimulators for hypoglossal nerve stimulation, the undefined supplemental fee ZE2022-187 can be negotiated by the hospital with the payers. The extra costs of the therapy are thus reimbursed on top of the DRG tariff.

- Reimbursement of nursing care

  Since 2019, the costs of nursing care are reimbursed separately from the DRG. The amount is calculated with the case-specific length of stay, the nursing care case weight per day in DRG 802C and the hospital-specific nursing care base rate (“Pflegeentgeltwert”).

This results in a total reimbursement for the implantation of the neurostimulator for the treatment of OSA with the HGNS of approximately € 5,976**Fehler! Textmarke nicht definiert.** plus supplemental fee (ZE2022-187) to be negotiated on a hospital-specific basis plus the case and hospital specific nursing care reimbursement.

The majority of in-patient treatment costs are caused by the material costs for the neurostimulation system. This includes all components of the system, which is used as a complete set during the in-patient stay for implantation. Thus, the actual on-site

[1] Undefined supplemental fees (ZE) are listed in the DRG catalogue without concrete tariffs. This means that the tariff for the ZE must be negotiated between the contracting parties on site.

[2] The amount is based on the data of the DRG catalogue 2022 and the federal base rate (Bundesbasisfallwert, BBFW) (calculated by InEK) of € 3,833.07 for 2022. According to sec. 10 KHEntgG (version valid as of January 1st, 2021), the BBFW must be published annually until March 31st. With a LOS beyond the LOS boundaries of the DRG 802C (4 and 24 days), deductions or surcharges have to be considered.

reimbursement depends largely on the amount negotiated for the undefined supplemental fee.

The amounts negotiated by the individual hospitals are not publicly available as summary and are often only known locally in individual hospitals. For this reason, reference is made here by way of example to the RWTH Aachen University Hospital, which – depending on the respective technology – indicates amounts between € 21,800 and € 28,000 for 2022 (70). These numbers are based on the total extra costs associated with the treatment in addition to the DRG tariff.

Furthermore, we refer to a cost-effectiveness analysis for the German healthcare system which puts the costs for the initial implantation (surgery and implant) of a neurostimulator for HGNS including a follow-up examination at € 26,184 ± 30% in 2016 (71).

8 Systematic literature research and selection

8.1 Question

The research question of the systematic literature search and review is divided into a question on efficacy (benefit) and a question on safety of the method for better clarity.

A) Question on efficacy:

Which level of efficacy is demonstrated at which level of evidence for the stimulation of the hypoglossal nerve (hypoglossal nerve stimulation, HGNS) with an implantable neurostimulation system in adult patients with moderate to severe OSA with respect to the parameters listed below, and how does the efficacy differ from the comparison group (if existing)?

Parameters for efficacy assessment:

- Daytime sleepiness (e.g. ESS)
- health-related quality of life (e.g. FOSQ)
- Cardiovascular events
- Mortality
- Adherence (e.g. average duration of nightly use)
- Apnea-hypopnea index (AHI)
- Oxygen Desaturation Index (ODI)
- Sleep architecture

If a comparison group is existing, only the comparison to no or conventional (best possible) conservative treatment (non-CPAP treatments) will be included. This means that HGNS will not be compared to the gold standard which is the positive airway pressure therapy (CPAP therapy). This definition was made because HGNS is only used when CPAP is not tolerated or ineffective (see ch. 6.5.4.1). A comparison with CPAP would therefore not reflect the current treatment in Germany, where both methods are used successively staggered. It would also be atypical to demand a strict "no treatment" for the comparison group, since the relevant patients are severely impaired and therefore usually do not accept abandoning therapy completely (at least over a longer period of time).

B) Question on safety:

Based on reported adverse events, what level of safety is demonstrated on which level of evidence for hypoglossal nerve stimulation with an implantable neurostimulation system in adult patients with moderate to severe OSA?

8.2 Inclusion criteria for literature selection

The inclusion criteria for the systematic literature review were defined using the so-called "PICOS" criteria. The acronym "PICOS" stands for the terms Population, Intervention, Comparison, Outcomes and Study type. The PICOS model is an instrument of evidence-based medicine. It is used to translate clinically relevant questions into a strategy for systematic literature research and subsequent selection of publications to answer the question. The criteria underlying the present systematic literature research and selection are listed in Table 8-1.

8.3 Literature research

To answer the research question, a systematic literature research has been conducted in two different literature databases:

- Medline via PubMed (last updated Sept. 19, 2021).
- The Cochrane Library[3] (last updated Sept. 19, 2021).

Based on the PICOS criteria two search strategies were developed specifically for each database. The documentation of the search and the search strategies are listed in the appendix.

The systematic literature search resulted in a total of 812 sources. Six additional publications were provided by the company Nyxoah S.A.

Accordingly, a total of 818 literature sources were included into the selection process.

[3] The Cochrane Library databases collection – Cochrane Central Register of Controlled Trials

Table 8-1: PICOS criteria for the systematic literature search and selection.

Population	Adult patients with moderate to severe OSA with intolerance or inefficacy or non-adherence to nightly positive airway pressure therapy. (Note: Studies in specific sub-populations that do not correspond to the typical care situation in Germany were not included (e.g. war veterans, patients with Down's syndrome).
Intervention	Stimulation of the hypoglossal nerve with an implantable neurostimulation system.
Comparison	No or conventional (best possible) conservative treatment (no hypoglossal nerve stimulation and no positive airway pressure therapy and no other surgical OSA treatment) - if a comparison group is existing.
Outcomes	
Efficacy	Improvement in OSA per daytime sleepiness (e.g. ESS), health-related quality of life (e.g. FOSQ), cardiovascular events, mortality, adherence, AHI, oxygen desaturation index (ODI), sleep architecture.
Safety	Adverse events: serious and non-serious events with or without association to the device, implantation procedure or stimulation.
Study type	
Efficacy	Meta-analyses, randomized controlled trials, non-randomized controlled trials, cohort studies, case series with at least 20 study participants, prospective and retrospective registry studies.
Safety	Meta-analyses, randomized controlled trials, non-randomized controlled trials, cohort studies, case series with at least 20 study participants, prospective and retrospective registry studies.

8.4 Literature selection

A total of 818 sources were included in the literature selection process according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) principle (72). Initially, three filter criteria were applied:

- Publication year 2011 or later

  The first pivotal study to achieve regulatory approval for one of the commercial stimulation systems was published in 2011.

- Language: German or English
- Full text available

  To allow a comprehensive understanding of the respective study, only full-text publications were included in the selection.

After applying the above filtering criteria, 473 sources remained in the literature selection.

In the next step, these were examined for duplicates. After excluding 30 duplicates, the remaining 443 sources were subjected to the further selection process. In the first step, sources on other topics (e.g. innervation of upper airway muscles) and other treatment methods (e.g. transcutaneous stimulation of the hypoglossal nerve) were excluded. Furthermore, sources were not included in the analysis for certain reasons. In particular, these included reasons of i) background literature (e.g. reviews), ii) inappropriate research question (e.g. contralateral tongue muscle activation in HGNS), or iii) inadequate study design (e.g. case report). The details of the selection process can be found in Figure 8-1.

As a result, 33 sources met the inclusion criteria (see ch. 8.2) and were assessed accordingly.

The six publications provided by the manufacturer were either duplicates (n = 4) or did not meet the inclusion criteria (n = 2).

The literature selection was performed independently by the authors (Susanne Habetha MPH, MD, and Sven Sauermann, MD). No automated support systems were applied. In case of discrepancies, these were resolved in a discussion either by consensus or by involving a third person.

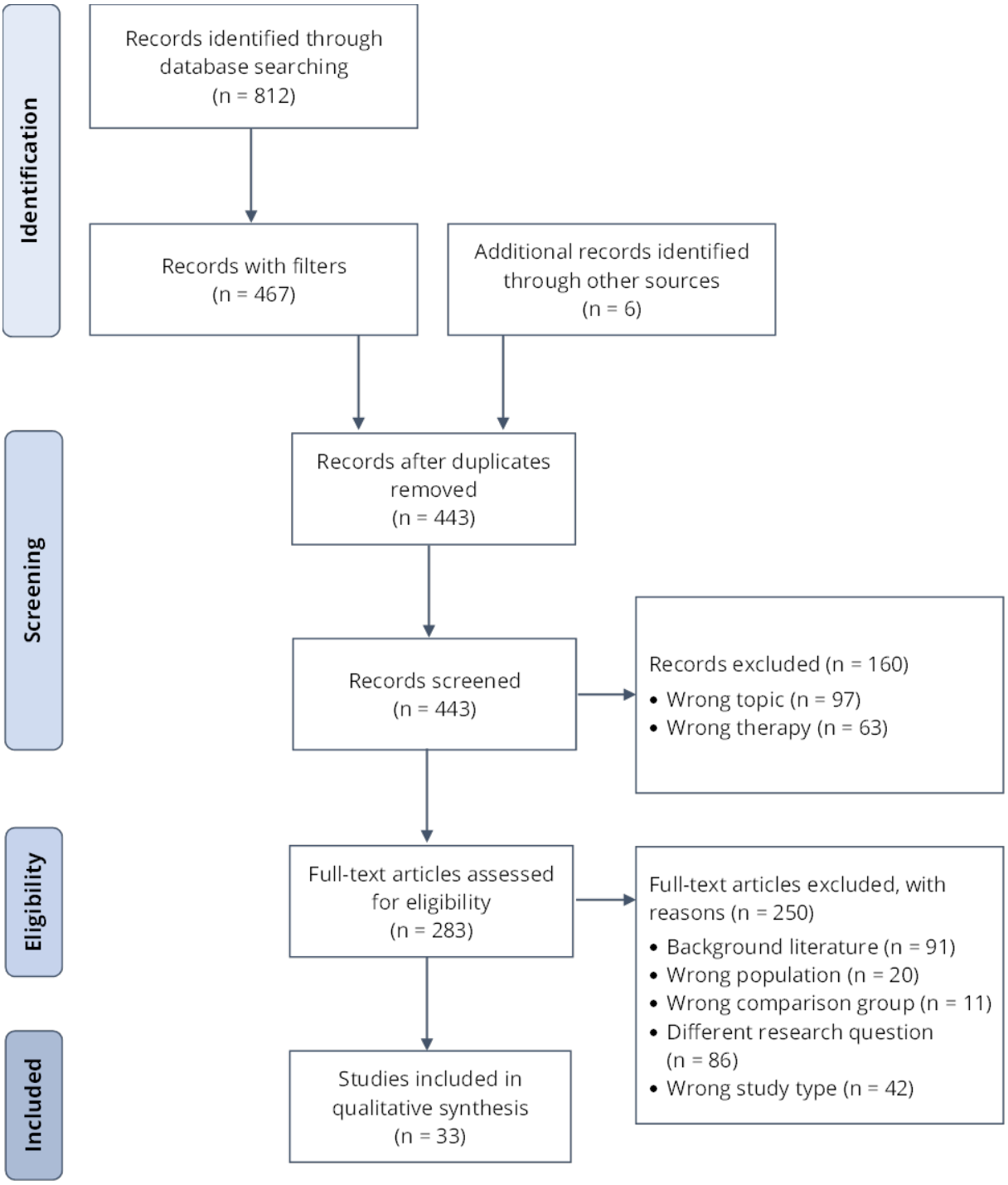
8.5 Supplementary research

To complement the systematic literature search in the Medline and The Cochrane Library literature databases, evidence-based expert reviews and guidelines were specifically searched on the following websites:

- AWMF Association of Scientific Medical Societies (http://www.awmf.org/) (Sept. 23, 2021)
- NIHR Health Technology Assessment Programme (https://www.nihr.ac.uk/ (Sept. 23, 2021)
- National Institute for Health and Care Excellence (http://www.nice.org.uk/) (Sept. 23, 2021).

A total of five (5) documents relevant to the indication under consideration were identified and included in the preparation of this document.

Figure 8-1: PRISMA flow chart showing the literature selection details.



9 Systematic literature review

The aim of this chapter is to present the systematic evaluation of the publications identified in the systematic literature research. To answer the research question, a total of 33 publications were identified (see ch. 8.4). First, the studies underlying each of the evaluated publications are classified according to their methodology with regard to the level of evidence in order to better assess the significance of the results. In the following, the results of the 33 evaluated publications on the endpoints defined in the research question are summarized.

Table 9-1 provides an overview of the publications evaluated and their relevant characteristics. In addition to the presentation in this chapter, a detailed description of the individual publications can be found in the appendix.

For the systematic literature review, data were extracted by one person (Susanne Habetha MPH, MD) and independently reviewed for completeness and accuracy by another person (Sven Sauermann, MD).

9.1 Assessment of the study quality

The validity of clinical studies is predominantly determined by the chosen study design, including the number of study participants. The standardized classification of studies is based on evidence levels according to certain methodological characteristics.

9.1.1 Basis of the assessment

The classification of evidence follows a uniform scheme in five levels, which – depending on the reference – may show differences in detail. A common classification of evidence levels is provided by the Oxford Centre for Evidence-based Medicine (73). This provides a differentiation of evidence on a total of ten levels (1a-c, 2a-c, 3a and b, 4, 5), which are defined depending on the type of object of investigation (e.g. therapy, diagnostics). The Federal Joint Committee (G-BA), in accordance with its rules of procedure, uses a somewhat less differentiated classification of seven levels of evidence (Ia and b, IIa and b, III, IV, V) for its benefit assessments of clinical methods to decide on the eligibility for reimbursement by the statutory health insurance (74). The basic quality requirements for the evidence of the individual levels are comparable in both classifications. In accordance with the objective of this systematic review in the context of service provision in the German healthcare system (see ch. 3), the following assessment of the included studies refers to the evidence levels according to the G-BA's rules of procedure.

Table 9-1: Overview of the evaluated publications and relevant characteristics.

Study Cluster	Number of publications (years)	Number of participants (initial) / countries (if indicated)	Max. observation period	Study design
Various individual studies	Publications: 11 (2011 - 2021)	475 / Australia, Germany, Netherlands, France, USA, Belgium	12 months (2), < 12 months (9)	RCT (1; n = 86), prospective single-arm study (6), retrospective study (3), case series (1).
STAR trial (Stimulation Therapy for Apnea Reduction)	Publications: 7 (2014 - 2018)	126 / USA, Germany, France, Netherlands, Belgium	60 months	Prospective single-arm study (6); RCT (1; n=46).
GPM Study (German Post-Market Study)	Publications: 6 (2017 - 2020)	60 / Germany	36 months	Prospective single-arm study
Meta-analyses	Publications: 3 (2015 - 2020)	6 studies with 200 patients; 12 studies with 381 patients; 9 studies with 350 patients; partially overlapping study populations	12 months	Systematic qualitative and quantitative evaluation of non-comparative studies
ADHERE registry (Adherence and Outcome of Upper Airway Stimulation (UAS) for OSA International Registry).	Publications: 4 (2018 - 2021)	Status 9/2020: > 2,000 patients enrolled in registry; 966 patients with 12-month follow-up; 717 patients evaluated in current study / USA, Germany	12 months	Retrospective and prospective registry study (3); non-randomized parallel-arm study (1; n=350).
MAUDE[4] database (Manufacturer and User Facility Device Experience database)	Publications: 2 (2020, 2021)	Total 312 reports of 330 adverse events / USA	05/2014 until 09/2019 and 01/2000 until 05/2020	Retrospective data analysis

9.1.2 Evaluation of the studies

The 33 publications systematically evaluated are based on several studies of different evidence levels. In a synopsis of the assessment criteria, the authors assign the evaluated evidence for HGNS to evidence levels Ib, IIb, and IV according to the classification of the G-BA (cf. Table 9-2 According to the authors, the three meta-analyses of non-comparative

[4] "Manufacturer and User Facility Device Experience (MAUDE) database" – database housing medical device reports submitted to the FDA

studies and the two retrospective data analyses of adverse events belong most closely to level IV, although this type of study is not explicitly mentioned in the inherent scheme.

Table 9-2: Assignment of the evaluated publications to the levels of evidence according to the rules of procedure of the G-BA (74)*.*

Evidence level	Definition	Publications
Ia	Systematic reviews of evidence level Ib studies	None
Ib	Randomized clinical trials	n = 2 (35,75)
IIa	Systematic reviews of evidence level IIb studies	None
IIb	Prospective comparative cohort studies	n = 1 (76)
III	Retrospective comparative studies	None
IV	Case series and other non-comparative studies	n = 25 single-arm cohort studies/registry studies/case series (19,41,42,44,47,58,77–95) n = 3 systematic reviews (96–98) n = 2 retrospective database analyses (60,99)
V	Observation of associations, pathophysiological considerations, descriptive presentations, individual case reports, opinions of recognized experts not supported by studies, reports of expert committees and consensus conferences	None (already excluded in the literature search)

The highest level of evidence achieved in the evaluated publications corresponds to level Ib of the G-BA, since two "randomized clinical trials" are available in which the efficacy and safety of the method were independently investigated (35,75). According to the evidence classification of the G-BA (s. Table 9-2), individual randomized controlled trials (RCTs) have the second highest quality after systematic reviews of RCTs, so that the results of the two evaluated RCTs have a correspondingly high value for the evaluation of hypoglossal nerve stimulation.

The two randomized trials are from 2014 (75) and 2021 (35) and differ with respect to some details of the trial design. In the study by Woodson et al. (75) patients were randomized into two parallel groups with and without stimulation and outcomes were measured after the duration of one week. The study by Heiser et al. (35) is a cross-over study, which means that patients switch from the intervention group to the control group or vice versa according to a predefined procedure, i.e., at the end of the study all study participants have received the therapy. This allows comparisons between groups and

within each group. The RCT by Heiser et al. (35) addresses some methodological limitations of the RCT by Woodson et al. (75) in order to increase the quality of the study and thus its significance. While the RCT of Woodson et al. (75) only included patients who were defined as "responders" – i.e. who could be successfully treated with HGNS – the RCT of Heiser et al. included and evaluated the treated patients regardless of the response to therapy (35).

Other advantages of the study by Heiser et al. include a low dropout rate, statistical strengths such as increased power, and the best possible blinding of patients, physician investigators and the research team (35). In fact, despite the use of a sham stimulation on a subtherapeutic level in the control group, blinding was limited because participants correctly estimated their group assignment in 92% and physicians correctly estimated the group assignment in 90% of the cases in a survey (35). This observation can be seen as a general limitation of the possibilities of blinding in connection with the use of HGNS. Depending on the stimulation system used, it is easy for patients to perceive, e.g. by the absence of certain movements of the tongue, if a subtherapeutic stimulation is performed.

The primary endpoints measured in the RCT by Heiser et al. were AHI on the one hand and daytime sleepiness on the other hand (35). Accordingly, this ensures valid results for the patient-relevant endpoint daytime sleepiness which is at the same time the leading symptom of OSA. Due to concerns of the ethics committee, the sham stimulation phase was not allowed to last longer than one week (35). Correspondingly, the investigation of long-term effects of OSA such as mortality and the occurrence of cardiovascular events was not possible in this short study duration (35).

A non-randomized, comparative study was conducted by Mehra et al. with a total of 350 participants in a parallel-arm study with and without HGNS treatment over a period of approximately one year on average (76). In this study, the treatment group is part of an international registry (ADHERE registry, see below).

The evidence evaluated is largely based on non-comparative prospective studies, resulting in 25 publications. These have a single-arm study design in which outcome parameters under treatment with HGNS are compared at different time points with baseline values before treatment. The study design of a prospective single-arm interventional study is often seen in the early phase of clinical application of a method. Because these studies are conducted without a control group, their validity to demonstrate a causal relationship between treatment and outcomes is limited from a methodological perspective.

Conducting a study at several treatment centers (multicenter) increases the generalizability and significance of the results (100). The vast majority of the single-arm prospective studies evaluated were conducted in a multicenter setting, with the study

centers usually also located in different countries, resulting in increased study quality in terms of greater generalizability of the results.

In addition, long-term results are already available for two different study populations from Germany and the USA. The observation period in the "German Post-Market Study", (GPM Study) is up to 36 months, whereby it should be taken into account that the outcome measurement after 24 and 36 months was voluntary and therefore patients with insufficient effect or use of HGNS are underrepresented compared to the overall study population (80). In the international STAR (Stimulation Therapy for Apnea Reduction) trial, outcome measurement at 60 months after neurostimulator implantation was voluntary with data collection from 71 of the initial 126 study participants. Possible bias due to the reduced number of participants at 60 months was excluded by various sensitivity analyses, including "best case" and "worst case" scenarios, to test the validity of the results (58).

With the three included meta-analyses, summary quantitative evaluations of different single-arm studies are available, which also allow assessment of the homogeneity or heterogeneity of the data. Since the study populations were partially overlapped in several meta-analyses, the results of the meta-analyses cannot be evaluated completely independently of each other.

It should be emphasized that registry data from numerous international treatment centers, i.e., data from the routine clinical application of HGNS – including in Germany – have already been collected and evaluated to a considerable extent in the ADHERE registry (Adherence and Outcome of Upper Airway Stimulation (UAS) for OSA International Registry, ADHERE). While on the one hand fundamental limitations of so-called "real world data" (RWD) regarding data quality have to be considered, on the other hand they form the basis to assess whether the results achieved in the context of a clinical study can also be achieved in routine care. Due to the consistency of the results from the registry data and the clinical trials with comparable inclusion criteria, the evaluated registry studies, especially the comparison of registry patients to patients without receiving HGNS (76), should be regarded as a meaningful addition to the evidence for HGNS.

In addition, two evaluations of the Manufacturer and User Facility Device Experience (MAUDE) database, an FDA database for reporting adverse events related to medical devices (60,99) provide a multi-year overview of the spectrum of potential adverse events associated with HGNS.

In summary, the total of 33 publications evaluated, including 25 prospective and three retrospective clinical studies with comparable inclusion criteria and more than 1,300 participants, including two RCTs with 46 and 86 participants, and one parallel-arm study, not only extensive evidence but also a high level of evidence is available to answer the research question.

9.2 Presentation of the study results

The 33 publications systematically evaluated show comparable outcomes overall in terms of type and extent. Since it does not seem purposeful to present all publications in the same detail in this chapter, a focus was placed on the higher-quality and more significant publications that are most likely to be used for evaluation by the responsible authorities in the context of a benefit assessment in the German health care system. Therefore, in particular the results of the randomized controlled trials by Heier et al. (35) and Woodson et al. (75), the non-randomized comparative study by Mehra et al. as well as the long-term data from the German Post-Market study (GPM Study) (80) and the STAR trial (58) are presented. In addition, registry data are included in the presentation, as they can provide information on the application of HGNS in clinical practice.

Some of the evaluated publications refer to the same study population over time. Since the long term assessment is particularly relevant for the treatment of a chronic disease and in order to avoid unnecessary multiple reporting of results, the most recent studies with the longest time course are considered in these cases. They are also expected to be the most significant ones due to their longer duration.

Unless otherwise stated, only statistically significant differences and changes are described in this chapter and presented as mean with standard deviation or 95% confidence interval (CI) and the p-value (p). Further information on the individual studies can be found in the comprehensive tabular summary of the 33 publications evaluated in the appendix.

9.2.1 Parameters for efficacy assessment parameters

The endpoints defined in the research question to assess the efficacy of HGNS treatment of OSA (see ch. 398.1) are presented separately in the following chapters. In addition, an introductory explanation is given for each endpoint and its significance.

9.2.1.1 Efficacy on daytime sleepiness

The abnormal fatigue of patients with OSA resulting from massively disturbed sleep is referred to as daytime sleepiness. Daytime sleepiness is not only the most common and important symptom of OSA (6) but also serves as a patient-reported outcome (PRO) to assess the therapeutic benefit in the treatment of OSA (101). For the measurement of daytime sleepiness, the validated Epworth Sleepiness Scale (ESS) questionnaire has been established (102). The ESS provides a score between zero and 24, with scores up to ten (10.0) being considered normal subjective sleepiness (103) and typically higher in OSA. A minimum clinically important difference (MCID) on the ESS can be defined as a reduction of the score by two to three points (104) or by two points (105).

Results on the patient-relevant parameter of daytime sleepiness can be found in 29 of the 33 publications evaluated. All results under HGNS treatment show scores in the normal range of the ESS between 5.3 ± 4.6 (80) and (19) 8.3 ± 4.4 (90) points.

The degree of improvement in daytime sleepiness for the treatment versus control group in the two randomized trials was highly significant at 4.5 (CI: 7.5; 1.4) points (p=0.005) (75) and 3.3 (CI: 4.4; 2.2) points (p<0.001) (35). Woodson et al. indicate that HGNS resulted in both significant and clinically relevant improvements in daytime sleepiness (75).

In the randomized trial by Heiser et al., the baseline daytime sleepiness score under HGNS treatment was 7.0 ± 4.4 points, within the normal range (35). The difference in change per group after one week of sham stimulation showed a large effect size (Cohen d of 1.07) as well as superiority (threshold value: 2 points) of therapeutic stimulation over sham stimulation with a highly significant difference of 4.6 (CI: 3.1; 6.1) points (p=0.001) between groups (35). Overall comparison of the scores of all 86 patients with treatment versus sham stimulation showed a highly significant increase in daytime sleepiness of 3.5 (CI: 2.6; 4.4) points (p<0.001) for sham stimulation (35). After cross-over of the study participants into the treatment or sham group, no carryover effect was detectable (p=0.23) (35).

Over the long-term course of the STAR trial, daytime sleepiness remained at a constant level within the normal range, with scores of 7.0 ± 4.0, 7.0 ± 5.0, 7.3 ± 4.9, and 6.9 ± 4.7 points at 18, 36, 48, and 60 months, respectively (44,58,82). For the scores at 12 and 24 months, an additional analysis revealed large effect sizes (defined as > 0.8) of 0.94 and 0.87 in each case (83). The proportion of patients with an ESS score within the normal range increased from 33% before treatment to 78% after 60 months of HGNS use (58). Also in the GPM Study, the improvement in daytime sleepiness did not show significant changes over the course to 36 months with scores in the normal range of 7.0 ± 4.5 (12 months), 5.3 ± 4.6 (24 months), and 6.0 ± 3.2 (36 months) (80). The results in studies of up to six months duration are in the normal range, e.g. 5.77 ± 3.35 (88) (minimum), 7.0 (81) and 8.0 (19), respectively 8.3 ± 4.4 points (90) (maximum).

The included meta-analyses calculated a highly significant improvement after 12 months of HGNS treatment of 4.8 (CI: 4.2; 5.4) points (96), 5.01(CI: 4.18; 5.83) points (98) and 4.42 (CI: 5.39; 3.44) points (97) (all p<0.00001).

The registry data show a highly significant reduction of the daytime sleepiness from initial pathologically elevated scores to 7.5 ± 7.4 points after four months (p<0.0001) (92) and 7.2 ± 4.8 points after 12 months (p<0.0001) (94) comparable effects in routine clinical practice as under study conditions. Compared to patients who did not receive HGNS treatment, daytime sleepiness of treated patients in the ADHERE registry improved on a highly significant and clinically relevant level after an average of 360 ± 171 days (7.2 ± 4.8 vs. 12.8 ± 5.2 points (p<0.001) (76).

9.2.1.2 Efficacy on health-related quality of life

Health-related quality of life represents another patient-relevant endpoint in the treatment of OSA (101) which can be used to evaluate the benefit of therapy. For the assessment of health-related quality of life, specific questionnaires are available for the different clinical areas. The validated questionnaire "Functional Outcome of Sleep Questionnaire" (FOSQ) was predominantly used in the evaluated publications, which proved to be suitable for documenting the sleep-related quality of life of patients with OSA (106). Scores below 17.9, with five to 20 possible points, indicate abnormal sleep-related quality of life (107). From a clinical perspective, the degree of improvement represents a relevant quality of life outcome, whereas a Minimum Clinically Important Difference (MCID) is not confirmed for the FOSQ (108). In their Cochrane Review, Kennedy et al. point to a one-point increase as a possible measure of clinically important improvement in the FOSQ (108).

Results on health-related quality of life as a patient-relevant endpoint are found in 21 of the 33 publications evaluated. In the synopsis of the studies, the quality of life increases with the duration of treatment, with values between 16.7 ± 2.2 (41) and 17.2 ± 3.0 points (19) after up to six months, between 17.0 ± 2.4 (47) and 17.5 ± 3.0 points (79) after 12 months and 17.2 ± 0.3 (standard error) (83) to 18.0 ± 2.2 points (58) after more than 12 months.

The percentage of patients with a value in the normal range increased over the long-term course from 15% before treatment to 67% after 60 months (58). The increase in quality of life was maintained to a clinically relevant extent and statistically significant over a 60-month period in the STAR trial (increase “as observed” at 60 months and using “multiple imputation”: 3.2 ± 0.3 (CI: 2.6; 3.8) points) (58). For the improvement in quality of life measured at 12 and 24 months, a large effect size (defined as > 0.8) of 0.91 and 1.00 was additionally found in the FOSQ total score, as well as moderate (defined as > 0.5) and large effect sizes for the individual five subscales of the questionnaire (83).

The difference between the groups with and without HGNS treatment in the subjective assessment of quality of life in the two RCTs reached clinically relevant and highly significant scores within one week at 2.1 points (CI: 1.4; 2.8, p<0.001) (35) and 2.9 points (CI: 0.8; 5.0, p=0.008) (75). The meta-analysis by Kompelli et al. found a highly significant increase in quality of life of 3.1 points at both six (CI: 2.6; 3.8) and 12 months (CI: 2.6; 3.7) (both p<0.00001) (96).

In the ADHERE registry, the mean quality of life after an average of 360 ± 171 days HGNS treatment in routine clinical care was documented to be 17.1 ± 3.2 points, scoring higher than a group of patients without HGNS treatment with 12.4 ± 3.7 points (after an average of 272 ± 278 days) with highest significance (p<0.001) (76).

9.2.1.3 Efficacy on cardiovascular events

Cardiovascular events such as myocardial infarction or stroke are relevant comorbidities of OSA and represent an additional risk in the context of the disease. Accordingly, they have direct relevance to patients and are considered a patient-relevant endpoint (101). Since cardiovascular events are based on long-term, chronic conditions and affect only a proportion of patients with OSA, studies over several years with large numbers of participants are required for investigation.

The 33 publications evaluated did not report cardiovascular events, which is consistent with the results of other literature reviews (11).

Currently, two evaluations in the STAR trial provide evidence that HGNS may have an impact on cardiovascular events: after 12 and 18 months, a reduction in blood pressure was observed in association with HGNS (75) and heart rate variability improved in all sleep stages with the use of HGNS (109).

In addition, studies show that especially the occurrence of OSA during REM sleep is associated with an increased risk of cardiovascular comorbidities (110). In the RCT by Heiser et al., OSA was highly significantly improved by HGNS both during REM sleep (decrease in AHI by -15.1 (CI: -19.7; -10.5) events/h), and during non-REM sleep**Fehler! Textmarke nicht definiert.**[5] (decrease in AHI by -15.7 (-18.5; -12.8) events/hour) (both: p<0.001) (35), also indicating that HGNS may reduce cardiovascular comorbidity.

High-level evidence on blood pressure and other cardiovascular parameters are expected from a double-blinded randomized controlled cross-over trial (CARDIOSA-12) comparing therapeutic versus sub-therapeutic stimulation, which will continue to recruit patients until the end of 2021 (111).

9.2.1.4 Efficacy on mortality

Mortality reflects the rate of fatal events within a defined period of time for a certain population, e.g. for a study population. For the so-called all-cause mortality, all fatal events are counted regardless of the cause. All-cause mortality (or overall survival) is considered a patient-relevant endpoint related to OSA (101). Disease-specific mortality includes only fatal events resulting from a specific disease. This can be used, for example, to measure the impact of the therapy under study on the number of deaths caused by the disease being treated.

The investigation of mortality is particularly challenging for long-term, chronic conditions such as OSA because large populations and very long observation periods are usually required to obtain meaningful results, which in turn implies a high potential for study bias.

[5] REM: Rapid Eye Movement; sleep is roughly divided into REM and non-REM stages, which alternate during healthy night sleep.

Mortality was not examined in any of the 33 publications evaluated.

9.2.1.5 Therapy adherence

Therapy adherence (or obsoletely referred to as compliance) is a prerequisite for effective treatment. The relationship between adherence and efficacy is particularly pronounced in the use of positive airway pressure, which is considered the gold standard for the treatment of OSA, and imposes corresponding limitations on therapy (24) (see ch. 6.4).

In HGNS treatment, therapy adherence can be recorded via documentation of nocturnal use. The frequency or duration of use can either be collected as subjective information from the patient or read out as objective usage data recorded by the currently available stimulation devices.

In 20 of the 33 publications evaluated, results on adherence are available, which refer on the one hand to the duration of application per night and on the other hand to the number of nights with application of HGNS. Overall, specific application times of an mean of 5.6 ± 2.1 (95) to 7.0 ± 1.9 hours per night (91) after 12 and three months are reported. In the meta-analysis by Constantino et al. the median daily use was 5.8 hours per night (98).

Long-term data are particularly relevant for assessing therapy adherence to identify whether the therapy is used in a way that achieves sustained efficacy. During the STAR trial, at 12, 36, and 60 months, 86%, 81%, and 80% of patients reported daily use of HGNS (58). In the GPM Study, the recorded objective duration of HGNS use per week also remained at a consistently high level of 40.3 ± 40.7 hours at 24 months and 41.0 ± 13.9 hours at 36 months, with 89.5% of patients using HGNS for at least 20 hours per week at 36 months (80). In addition, Hofauer et al. did not find a correlation between the occurrence of side effects and adherence to HGNS (78).

Objective usage data recorded by the neurostimulation devices in the ADHERE registry in 382 patients during routine care show an average usage time of 5.6 ± 2.1 hours per night 12 months after implantation (94). Regarding the frequency of use per week, after six months, use of more than five nights per week is reported in 91% of patients (19) and after 12 months a mean usage of 6.8 ± 0.9 nights per week (78) is reported.

9.2.1.6 Efficacy on the Apnea-hypopnea index (AHI)

The AHI indicates the mean number of apnea and hypopnea events of at least 10 seconds duration each related to one hour of sleep time (4). In the studies evaluated and in the scientific literature reviewed by the authors, the AHI is a central parameter for measuring the severity of OSA. The diagnosis of OSA starts from values of 5 events/hour (4). According to Suurna et al., using the AHI to measure treatment success is fraught with challenges (112). At the same time, the AHI is currently considered the best objective

measure of treatment efficacy for OSA (23) and is used in sleep medicine research as the so-called "Sher criteria" for measuring treatment success (113):

- Reduction of AHI by at least 50% and an absolute AHI below 20 events/h.

The independent German Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG), which conducts benefit assessments on behalf of the G-BA, considers the AHI not to be patient-relevant and an unvalidated surrogate endpoint that is not suitable for assessing the benefit (101).

Due to the consistent use of the AHI as a central endpoint in clinical studies over decades and not least because the AHI is used to classify the severity of OSA (see ch. 5.2), the AHI has a relevant meaning for clinical practice in the evaluation of therapeutic success in the treatment of OSA and is therefore also reported here.

Data on AHI are found in 30 of the 33 publications evaluated, all of which showed significant improvement in AHI with HGNS treatment. In the two randomized trials, the AHI worsened under sham stimulation (35) or discontinuation of stimulation (75). The difference between treatment and sham stimulation or discontinuation of treatment was highly significant in both trials and was -15.5 (CI: -18.3; -12.8) events/h ($p<0.001$) (35) and -16.9 (CI: -24.7; -9.0) events/h ($p<0.001$) (75). In the study by Heiser et al. after the first week, 33 of 45 patients (73.7%) with therapeutic stimulation were classified as responders (defined as AHI ≤ 15 events/h) and 13 of 44 patients (29.5%) with sham stimulation (35).

The randomized trial by Heiser et al. demonstrated improvement in AHI independent of patient position (supine and other positions) and across all sleep stages (non-REM (N1, N2, N3) and REM sleep[6]) (35). Cross-over of study participants to the therapeutic or sham stimulation group was not associated with any carryover effect ($p=0.55$) (35).

In the GPM Study, the AHI at 36 months averaged 13.1 ± 14.1 events/h, unchanged from measurements at 12 and 24 months ($p=0.54$) and significantly improved from baseline ($p<0.05$) (80). At 60 months, the AHI in the STAR trial was 12.4 ± 16.3 events/h, the same significantly improved level as at 12 months (15.3 ± 16.1 events/h) and 36 months (11.5 ± 14.0 events/h) (58). In addition, at 60 months, 75% of patients met the Sher criteria of successful treatment (58). In publications with 12 months of observation, the values for the AHI are significantly reduced in the range between a mean of 7.1 ± 5.9 (86) and 25.3 ± 20.6 events/h (47) and in studies with observation periods of up to six months, significantly improved values between 1.2 ± 1.1 (91) and 25.4 ± 23.1 events/h (90) are achieved.

Three meta-analyses confirm consistently significant improvement in AHI, with no evidence of heterogeneity due to different stimulation technologies (96–98). ADHERE registry data show an AHI of 14.2 ± 15.0 events/h after 12 months of follow-up, confirming

[6] REM: Rapid Eye Movement; sleep is roughly divided into REM and non-REM stages, which alternate during healthy night sleep.

transferability of the study results to routine clinical practice (94). The non-randomized comparison of patients from the ADHERE registry with patients without HGNS showed a highly significantly greater improvement in AHI of -19.1 ± 15.8 after an average of 360 ± 171 days in the registry patients compared to -8.1 ± 20.9 events/h after an average of 272 ± 278 days in the group without HGNS (p<0.001) (76).

9.2.1.7 Efficacy on the Oxygen desaturation index (ODI)

One of the consequences of the impaired breathing in OSA is that the oxygen saturation in the patient's blood decreases, which in turn leads to harmful effects in different parts of the body (see ch. 5). The oxygen desaturation index (ODI) indicates the mean frequency of events per hour of sleep in which the blood oxygen level drops by a value of 4% or more and is thus used to document the immediate effects of reduced breathing.

IQWiG, which is responsible for benefit assessments in Germany, does not consider the ODI in the context of OSA to be either a patient-relevant endpoint or a validated surrogate endpoint that cannot be used to prove the benefit of a therapy (101). In contrast, specialized sleep physicians attribute a relevant meaning to the ODI for assessing the treatment success based on the sleep medical research on HGNS (112).

The authors consider the ODI to be a widely used and relevant objective measure of the effects of airway obstruction in the scientific literature over decades and have therefore included it as another parameter, in addition to the AHI, for assessing the severity of OSA.

In 23 of the 33 studies evaluated, data were provided on ODI, for which there was consistently a significant improvement with treatment with HGNS. In the cross-over RCT, switching from therapeutic to sham stimulation resulted in an increase in ODI by a mean of 12.7 (CI: 10.3; 15.2) events/h with a highly significant difference between groups of -12.2 (CI: -14.8; -9.6) events/h (p<0.001) (35). After the one-week therapy withdrawal in the study by Woodson et al. the ODI was 23.0 ± 15.6 events/h, back to the baseline level before the start of HGNS, and the difference between groups was highly significant at -15.1 (CI: -22.7; -7.5) events/h (p<0.001) (75).

The long-term data show significantly (p<0.05) improved values at a constant level of 11.4 ± 11.5 and 11.6 ± 14.0 events/h after 24 and 36 months (p=0.69) in the GPM Study (80) and in the STAR trial of 9.1 ± 11.7 and 9.9 ± 14.5 events/h at 36 and 60 months (58). Compared with baseline, the results of the 12-month studies showed significantly reduced values ranging from 9.9 ± 8.0 (86) and 15.7 ± 19.6 events/h (47) and for observation periods up to six months, the significantly reduced ODI ranges from 9.1 ± 16.7 (41) and 23.6 ± 22.3 events/h (90).

The three meta-analyses confirmed the significant reduction in ODI in the absence of evidence for heterogeneity due to different stimulation technologies (96–98). The reduction in ODI in each of the quantitative analyses at 12 months was -13.73

(CI: -16.87; -10.58) events/h (p<0.0001) (97), -15.01 (CI: -17.35; -12.68) events/h (p<0.00001) (96) and -14.79 (CI: -17.26; -12.32) events/h (p<0.00001) (98).

Patients in the ADHERE registry had a highly significant lower ODI (14.1 ± 14.1 vs. 25.5 ± 17.9 events/h (p<0.001)) after an average of 360 ± 171 days compared to patients not treated with HGNS (76).

9.2.1.8 Efficacy on sleep architecture

Sleep architecture is built by the different sleep stages and their sequences as well as complementary factors. The main sleep stages are rapid eye movement (REM) and non-REM sleep, the latter being further subdivided into three stages: i) N1 sleep (falling asleep), ii) N2 sleep (stable sleep), and iii) N3 sleep (deep sleep). Sleep architecture has an altered pattern in OSA with increases in phases of "lighter sleep" (stage N1) and decreases in deep sleep and REM phases (87).

The wake-up reactions typical of OSA as a result of reduced breathing (arousal) disrupt the normal sleep architecture. The frequency of these wake-up reactions is measured as the so-called arousal index. The arousal index is the most frequently investigated parameter in connection with sleep architecture in the evaluated studies and is reported in 11 publications with consistent improvement of the values. Data on other parameters of sleep architecture can be found in six publications.

In the RCT by Woodson et al. the one-week interruption of HGNS resulted in a highly significant difference in arousal index between groups of -17.7 (CI: -25.8; -9.6) events/h (p<0.001) in favor of HGNS (75). In the RCT by Heiser et al. the arousal index was lower in the treatment group (1.9 (CI: 1.1; 4.8) events/h) than in the sham stimulation group (2.2 (CI: -0.7; 5.2) events/h), however the difference did not reach statistical significance (p=0.861) (35).

In the long-term data, the highly significant reduction of the arousal index remains with a highly significant decrease from an initial 27.8 ± 117 to 7.8 ± 9.7 events/h (p<0.0001) at 60 months (58). Hofauer et al. showed a highly significant improvement of the arousal index for all sleep stages after two months with an improvement from 24.3 ± 15.1 to 15.2 ± 9.8 events/h (p=0.002) and the reduction of arousals especially in the N1 and N2 sleep as well as a significant decrease of the proportion of N1 sleep (falling asleep phase) and a significant increase of REM sleep time (77). In further studies, the arousal index decreased highly significantly after six months by 12.7 (CI: 16.6; 8.9) events/h (p< 0.0001) (19) and 11.1 ± 19.0 events/h (p<0.001) (90) as well as after 12 months from 44.3 ± 17.7 to 27.5 ± 13.4 events/h (p<0.001) (47).

Other positive effects on sleep architecture, particularly a reduction in lighter sleep (N1 sleep) and an increase in REM sleep, were shown in several studies (19,41,47,77,84,87), but were not consistent across all studies evaluated.

9.2.2 Safety results

During clinical trials, adverse events are documented to assess the safety of a therapy. Adverse events (AE) and serious adverse events (SAE) (e.g. life-threatening events or events requiring/prolonging hospitalization) are differentiated.

In this chapter, serious and non-serious events with or without relation to the device, the implantation procedure or stimulation are presented in accordance with the research question for the present literature review (see ch. 8.1). In HGNS, AEs related to the treatment (stimulation) and/or the medical device (neurostimulator) can be divided into intraoperative and postoperative AEs related to the implantation of the neurostimulator and events related to long-term stimulation treatment.

Adverse events were reported in 26 of the 33 publications evaluated. Of these, 18 publications have an observation period of 12 months or more (up to 60 months), so that results on the implantation procedure as well as on the permanent use of the stimulation in the patient's daily life are available. In addition, two evaluations of the Manufacturer and User Facility Device Experience (MAUDE) database, an FDA database for reporting adverse events related to medical devices (60,99) provide an overview of the spectrum of possible AEs associated with HGNS.

In HGNS, mild and moderate AEs are most common across all studies, whereas SAEs are rare. The most common non-severe AE in the STAR trial long-term results was discomfort due to electrical stimulation, which occurred 81 times related to 126 patients within the first year after implantation and in most cases resolved after patients acclimated to the treatment or could be resolved by adjusting the stimulation parameters (84,114). Similarly, in evaluations of the ADHERE registry, the most common AE was stimulation-related discomfort, occurring in 12% and 8% of patients (after titration and after 12 months) (94) and in 7% of patients (after titration) (92).

Tongue abrasion is caused by the movement of the tongue against the teeth and are also one of the common non-serious AEs (96). They resolved in the STAR trial either when patients acclimated to therapy, with adjustment of stimulation parameters, or use of a toothguard (84). In the meta-analysis by Kompelli et al., other AEs mentioned were abnormal sensations, paresthesias, change in salivary flow, and lip weakness (96).

Over the long-term, the number of all adverse events related to treatment or the stimulation system decreased from a total of 279 in the first year to 20 events in the fifth year in 126 study participants in the STAR trial by the end of the 60-month observation period (58). Study periods of up to six months also show that initial AEs resolved almost complete (19,81,90). At three and six months, 90.2% and 85.2% of patients had no adverse events in a study by Eastwood et al. (41).

Adverse events related to the surgical implantation of the neurostimulator have been reported with varying frequencies, e.g. 3% in 250 patients in the ADHERE registry (76) and

71% in 21 patients (41). In particular, these are events expected with surgery, such as pain, swelling, hematoma, seroma, or injury of a blood vessel (99). In the STAR trial, AEs related to the surgical procedure (e.g. pain, weakness of the tongue, effects due to intubation) occurred in 88% within the first 30 days after implantation (84). In a review of 219 patients documented in the ADHERE registry, 7 patients were affected by postoperative AEs, all classified as mild (71.4%) or moderate (28.6%) (76).

The only adverse event reported in the RCT by Heiser et al. was stroke during the phase of therapeutic stimulation (35).

Infections are among the rarer AEs in the clinical trials evaluated, whereas they are the most common reason for neurostimulator explantation in the MAUDE report analysis (60,99). Infections required different measures depending on their severity, up to revision surgery (90) or explantation of the neurostimulator (19).

Malfunction or dislocation of individual components of the neurostimulation system, e.g. the electrodes, could be corrected across technologies by revision surgery with replacement or repositioning of the corresponding device part (41,90,114). In a study with bilateral stimulation, no SAEs related to the neurostimulator occurred within six months (19).

Within 60 months, a total of nine SAEs related to the stimulation system were reported in eight patients (6% of 126 study participants), which were resolved by repositioning of the sensing or stimulation lead or replacement of appropriate parts (58). In the GPM Study, two serious AEs were reported in two of the initial 60 patients and 38 patients still participating after 36 months, which were resolved by replacement of the sensing lead (80). In the ADHERE registry, revision surgery to reposition the stimulation electrode was successfully performed in a total of three cases at six months (640 patients) and 12 months (382 patients) (94). In other studies, no SAEs occurred in periods up to 12 months (86–88,92).

Technology-specific AEs reported with unilateral, breath-controlled stimulation were pneumothorax, pleural effusion, and migration of the sensing lead into the pleural space (60,99). With bilateral, cyclic stimulation, skin irritation due to nocturnal application of the external energy source occurred, which resolved in most cases without or with local treatment (19).

In the 33 publications evaluated, no deaths related to HGNS treatment or the neurostimulation system were reported. In the GPM Study, after 36 months of observation, one fatal event unrelated to the neurostimulator is stated (80). In the STAR trial, a total of five fatal events are reported after 60 months of observation time (58). The causes of death are reported as i) “sudden death”, ii) “cardiac arrest after a fall and blunt chest trauma”, iii) “homicide”, iv) “malignant melanoma”, and v) “myelodysplastic syndrome” (58).

10 Therapeutic gap in the treatment of obstructive sleep apnea

The current recommendations for the therapy of obstructive sleep apnea according to the S3 guideline of the German Sleep Society (Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM) (3,4) are presented in chapter 6. Accordingly, the gold standard is the continuous positive airway pressure (CPAP) therapy. This can be supplemented by various non-surgical and surgical methods, including the hypoglossal nerve stimulation. In order to clearly distinguish HGNS linguistically from the other surgical treatment alternatives that are not neurostimulation procedures, these will be hereafter referred to as "conventional surgical procedures" in reference to the designation by Heiser and Hofauer (5).

Many patients with OSA cannot be treated adequately with the available methods in addition to CPAP for first- and second-line therapy based on multiple limitations (see following chapters). Therefore a new treatment alternative is required (32,33,115). In particular, the limited adherence to CPAP as first-line therapy is a challenge in the treatment of OSA. Dedhia et al. concluded that a large proportion of patients are not adequately treated with CPAP, and thus symptoms and cardiovascular risks persist (32). This means that a significant gap in healthcare provision exists in the treatment of patients with OSA.

The method of HGNS can contribute significantly to closing this therapeutic gap due to its special characteristics as a neurostimulation procedure. According to Heiser and Hofauer, the treatment of OSA with HGNS closes a gap between the "non-invasive procedures" and the "conventional surgical procedures" (5).

In the following chapters

- the therapeutic gap in the treatment of OSA based on the limitations of positive airway pressure therapy and other conservative therapies as well as conventional surgical therapies is explained in detail
- it is justified, based on the systematically evaluated evidence, why the HGNS fills a therapeutic gap in the provision of healthcare to patients with OSA in Germany.

10.1 Limited efficacy of positive airway pressure therapy due to poor adherence

Continuous positive airway pressure (CPAP) therapy has been available for several decades as the gold standard or first-line therapy in the treatment of OSA (4,22,27). Despite this effective, non-invasive, and "relatively cost-effective" (20) method, there is a

considerable challenge to the treatment of OSA due to limited patient adherence to CPAP (see ch. 6.4).

The lack of adherence results from the fact that patients either use positive airway pressure

- in an inappropriate manner and it is thus ineffective, or
- discontinue the therapy completely.

In both cases, the symptoms of OSA persist unchanged (30). For example, many patients discontinue CPAP so early during the night that the effect on certain stages of sleep is absent in the morning hours, which impairs the treatment (5). Thus, these patients are not adequately treated despite the use of CPAP.

Summarizing the results from the literature, adherence to CPAP is approximately 50% (22,115). Mashaqi et al. give a range of 20% to 80% for adherence to CPAP (11). This means that about half of the patients cannot be successfully treated by CPAP and continue to suffer from the disease. Additionally, avoidable costs are incurred due to the persistence of OSA and associated comorbidities. This highly relevant limitation of therapy could not be eliminated neither by further development of the techniques and devices used for CPAP nor by more comfortable masks (26).

10.2 Limitations of further therapies

Both conservative, so-called non-CPAP procedures, and various conventional surgical procedures are used as complementary or second-line therapies for the treatment of OSA.

Currently, there is no generally accepted second-line therapy available for ineffective CPAP treatment (3,4,32). Second-line therapy is selected from alternative treatment options, depending on individual findings, and is often used as combination therapy (32). According to the S3 guideline (in addition to HGNS), treatment with mandibular advancement devices (MAD), weight reduction, positional therapy and conventional surgical procedures play a role (3,4).

Many patients cannot be adequately treated despite the various therapeutic options available in addition to CPAP and next to HGNS for the reasons outlined here, so that symptoms and health risks persist (32). This is related to the specific limitations of the therapies, which are explained in the following.

10.2.1 Limitations of conservative therapies

Mandibular advancement devices (MAD)

For conservative treatment with MAD, the main limitations are the selection of patients and compliance with the conditions for health service provision defined by the Federal Joint Committee G-BA (21). According to the S3 guideline, MAD are less suitable for the treatment of severe OSA (AHI > 30 events/h) and obese patients (BMI > 30 kg/m²) (4). According to international studies, the evidence on efficacy and adherence shows mixed results (34,116) and in some cases only a small effect on symptoms (117).

The G-BA recently admitted treatment with MAD to reimbursement by the statutory health insurance if CPAP cannot be performed successfully, whereby extensive conditions regarding patients selection and treatment must be met in this case (21). Accordingly, treatment with MAD must be carefully considered in individual cases and can be expected to be effective for a certain selection of patients in compliance with requirements defined by the G-BA (118). Thus, this conservative therapy can be included as an option in the therapy selection, in particular before the implementation of more invasive treatment methods, based on the evaluation of the G-BA.

Positional therapy

Positional therapy is appropriate only for a sub-group of approximately 25% to 30% of patients with OSA whose OSA requires treatment exclusively in the supine position ("supine-dependent obstructive sleep apnea") (3). In addition, it should be kept in mind that the procedures or medical aids used show considerable differences in the reliability of preventing supine position (3). In addition, adherence in the case of subjectively perceived discomfort represents a major limitation (119).

Weight reduction

According to the S3 guideline, a reduction in body weight has a positive effect on OSA, but often only causes an improvement and not an elimination of OSA (4). Furthermore, weight reduction measures are subject to "fundamental limitations" (4). Particularly challenging are the maintenance of successful weight reduction and the need for a high level of personal commitment and effort (4).

10.2.2 Limitations of conventional surgical procedures

Conventional surgical procedures aim to treat the obstruction by permanently altering the anatomy of the upper airway and are thus irreversible treatment procedures, unlike hypoglossal nerve stimulation. Depending on the location of the obstruction, procedures are distinguished at different levels of the upper airway (e.g. soft palate or base of the tongue) (120). For example, in the case of obstruction caused by enlarged tonsils (tonsillar

hyperplasia), tonsillectomy can be performed (3). For patients without a corresponding anatomical finding, these procedures are out of consideration (3).

At the same time, the irreversible changes to the patient's anatomy represent a major limitation for conventional surgical procedures. This is because the surgical intervention can lead to undesirable effects that, due to the irreversible changes, can potentially mean lifelong impairments for the patient and result in the need for additional treatment. It follows that the indication should be made all the more carefully, especially since the evidence, especially on long-term efficacy, is limited both in scope and quality (23,120–122).

Success rates for conventional surgical treatment were reported to range from 48% or 64% (uvulopalatopharyngoplasty) to 77% (maxillo-mandibular advancement), depending on the procedure and the study period (116). In contrast, the potential risks and long-term morbidity due to side effects are high in contrast to HGNS, especially for uvulopalatopharyngoplasty and uvulopalatoplasty (121). Common long-term side effects include difficulty swallowing, globus sensation, and voice changes (3,121).

The individual conventional surgical procedures each treat localized indications, although obstruction often occurs at multiple levels of the upper airway (5). Therefore, surgical procedures are also used in combination and are referred to as multilevel surgery (34). Due to the high invasiveness and morbidity of combined procedures in particular, these are increasingly losing importance in Germany with limited patient acceptance (34).

The limitations of conventional surgical procedures due to their risks and incomplete evidence are also presented in the updated S3 guideline and are reflected in the restrictive note that the therapies should be considered "especially when other therapy (CPAP, MAD) is not possible or is not tolerated adequately" (3).

Surgery to improve nasal breathing serves only indirectly to treat OSA. If the acceptability of CPAP is limited by obstructed nasal breathing, it can be increased by surgery to improve nasal breathing (3).

10.3 Hypoglossal nerve stimulation closes a therapeutic gap

For patients who cannot benefit from CPAP, a decision on alternative treatment must be made individually based on the respective indication criteria, prospects of success, and risks of further therapies. Here, HGNS offers an option for long-term effective and safe treatment for patients with moderate to severe OSA (58,80,123). Heiser and Hofauer see the advantages of HGNS in the low invasiveness and subsequent adjustability (titration) of the therapy with higher acceptance by the patients than for "other surgical interventions" (5). At the same time, HGNS is superior to CPAP in terms of adherence (11). The HGNS represents according to Whelan and Soose a "hybrid" therapy composed of

surgical implantation of the stimulator and conservative therapy optimization and thus closes a therapeutic gap in the care of suitable patients (124).

The view that HGNS is an effective addition to therapeutic options for the treatment of OSA is shared in numerous publications (e.g. (11,22,32,37,125,126)). It is based on the available evidence, which represents the efficacy and safety of the method and its defined field of application within 10 years of the use of HGNS with commercial implantable stimulation systems. The systematic review of the 33 systematically searched publications presented here provides a comprehensive overview of the study results (see sch. 9 and Appendix).

An additional advantage of HGNS is that it can be combined with other therapies, such as weight loss, positional therapy, or MAD, to increase the efficacy of treatment (124).

In the following, the importance of HGNS for the treatment of OSA is illustrated by some essential aspects.

10.3.1 Patient perspective

The patient perspective is particularly relevant for the success of treatment in chronic diseases such as OSA. The example of CPAP shows that a generally effective treatment method must be accepted and applied accordingly in order to treat a disease effectively. The patient's perspective plays an important role due to the limited adherence to CPAP (see ch. 10.1), especially in the treatment of OSA.

10.3.1.1 Benefit for the patient

In clinical trials, the patient perspective is particularly reflected in so-called patient-relevant (patient-reported) outcomes (PROs). According to the G-BA's rules of procedure, PROs are of great importance in the context of benefit assessment procedures and serve to "assess the therapeutic benefit" (74). The German independent Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG), which is commissioned by the G-BA to conduct the corresponding benefit assessments, has defined patient-relevant outcomes in the context of OSA (101). The systematic literature review in this document is based on these endpoints.

In addition to adverse events and mortality, relevant PROs include daytime sleepiness as a leading symptom of OSA as well as health-related quality of life (101). Daytime sleepiness and quality of life have been investigated in the vast majority of systematically evaluated publications and uniformly show values in the normal range or significant and clinically relevant improvements under treatment with HGNS (see chs. 9.2.1.1 and 9.2.1.2). With the clear efficacy on these patient-relevant endpoints as well as the improvement in

quality of life described in chapters 9.2.2 and 10.3.4, there is sufficient evidence for PROs to consider HGNS as a beneficial treatment option from the patient perspective.

10.3.1.2 High adherence to hypoglossal nerve stimulation

In patient surveys it was shown that the patients themselves evaluate the HGNS treatment very positively (76,78,94,95). This positive attitude of the patients is probably responsible for the good adherence to the treatment with HGNS. This can be seen, for example, in long-term data with daily use in 80% of patients after five years (58) or an average duration of use in the range of five to seven hours per night after 12 months (see ch. 9.2.1.5) which is consistent across the different studies. Thus, the values for minimum use of CPAP (≥ 5 nights/week and ≥ 4 h/night) are clearly exceeded by the majority of patients. It has been shown that the perception of stimulation or associated discomfort does not reduce the use of HGNS (95). Adherence to the method of HGNS is consistently high across technologies (19,41,47,80).

10.3.2 Advantages of HGNS compared to conventional surgical procedures

HGNS differs from conventional surgical procedures because it treats obstruction at several airway levels simultaneously with only one – comparatively minimally invasive – procedure (32,36–38,124). Retrospective comparison of 233 patients treated with conventional surgery (68% palatal procedures, 31% multilevel procedures, <1% isolated tongue base procedures) and 465 patients treated with HGNS from the ADHERE registry showed a significantly better outcome for HGNS in terms of AHI and surgical success according to Sher[7], with a mean decrease in AHI of 21.4 ± 17.8 vs. 15.9 ± 17.3 events/h ($p<0.001$) or a success rate of 70% vs. 48% ($p<0.001$), and a comparable improvement in daytime sleepiness (127). In a recent meta-analysis of five publications with a total of 990 patients, HGNS shows better results in terms of objective endpoints (e.g. AHI) and comparable results in the patient-relevant endpoint of daytime sleepiness compared to common and newer conventional surgical procedures (uvulopalatopharyngoplasty, expansion sphincter pharyngoplasty, transoral robotic surgery (TORS), surgery at the palate or base of the tongue) (128).

Because the neurostimulator is implanted outside the pharynx, the risks of conventional surgical procedures such as pain, bleeding, difficulty swallowing, and changes in taste are minimized with HGNS, and HGNS is associated with faster postoperative patient recovery (128). It has been shown that difficulty swallowing and voice changes, which have been described with other surgical therapy methods, such as uvulopalatopharyngoplasty (23) can be avoided with HGNS (129,130). In the literature included in the present systematic review, serious adverse events associated with HGNS were rarely described, and the mild

[7] Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/hour) (113).

and moderate adverse events occurred predominantly temporarily at the beginning of the therapy (see ch. 9.2.2).

Furthermore, HGNS differs from conventional surgical procedures because of the possibility to further control and optimize therapy after surgery and thus also to positively influence adherence. This is done in the context of long-term sleep medical follow-up by titrating the stimulation parameters, which can and should be performed regularly and at any time as needed to optimize the therapy and adapt it to changed conditions, if necessary (5). This permanent possibility to influence the therapy is especially relevant for chronic diseases like OSA (32).

Another essential and especially from the patient's point of view relevant difference to conventional surgical procedures is that the implantation of the neurostimulator does not cause any permanent anatomical changes and the stimulator can be removed again (58–60).

10.3.3 Relevance of correct indication for hypoglossal nerve stimulation

Careful patient selection represents a major factor influencing the long-term treatment outcome of HGNS (37). Over the past decade of using HGNS, patient selection criteria have been investigated in numerous studies. Specifically, the criteria examined include baseline AHI and BMI, age, prior surgical treatments, and upper airway collapse pattern.

According to the S3 guideline, HGNS (among other criteria) should only be used in patients with an AHI between 15 and 65 events/h and a BMI up to 35 kg/m² (3). Based on initial study results (84), the indication criteria with respect to AHI and BMI were initially more narrowly defined: AHI between 20 and 50 events/h and BMI below 32 kg/m². The results from further studies (19,79,86,131) show that a slight expansion to the current thresholds is possible without compromising efficacy or safety.

With respect to patient age, it has been shown that older age (≥ 65 years) correlates with a higher probability of treatment success and adherence (131). At three German treatment centers, a comparison of patients up to 64 years and as of 65 years showed an equal improvement in the severity of OSA in both groups based on the parameters AHI and ODI as well as the symptom of daytime sleepiness, whereas patients as of 65 years used HGNS more often (132). Thus, HGNS can be used effectively in older patients as in younger patients.

Several studies show that HGNS is also effective in patients previously treated with conventional surgical procedures mainly in the soft palate (e.g. uvulopalatopharyngoplasty) (91,133,134). This means that a conventional surgical pre-treatment of OSA is in principle not a contraindication for the use of HGNS.

For unilateral breath-controlled stimulation technology, it is necessary to exclude a complete concentric collapse (CCC) of the upper airway at the soft palate, as the expected

efficacy is not achieved with this indication (3). Sleep endoscopy provides an effective and feasible diagnostic procedure to exclude CCC of the upper airway (see ch. 6.5.4.2). Furthermore, this diagnostic method provides information about the details of the individual condition and is generally considered a useful tool to optimize therapy selection (135,136).

In addition, other factors must be taken into account when determining the indication in individual cases (see ch. 6.5.4). These include certain pre-existing conditions, the patient's individual willingness and ability for long-term use of HGNS, and technical characteristics of the various stimulation systems. For example, in the case of a medical need for regular whole-body magnetic resonance imaging (MRI), HGNS can be applied with bilateral cyclic stimulation technology (55), whereas MRI with other stimulation technologies is not possible or only possible to a limited extent.

10.3.4 High safety level of hypoglossal nerve stimulation

The systematically evaluated studies and registry analyses show consistent results with respect to a high safety of treatment with HGNS (see ch. 9.2.2). Studies in different age groups show that the high safety level of HGNS is also achieved in patients aged 65 years and older (132,137). This means that treatment of this age group with HGNS does not entail increased risks.

Serious adverse events related to the treatment or neurostimulation system are rare, regardless of the technology used (19,58,90). In addition, product-related safety for the individual systems has been demonstrated in the context of CE mark and has been sufficiently investigated in studies as well as registry data (see ch. 9.2 and Appendix). Long-term data show that serious adverse events related to the treatment or the neurostimulation system – even over several years – are rare (58,80). In the studies evaluated, device migration, malfunction, or misplacement of electrodes or the pulse generator were mentioned most frequently. These events can be corrected by various measures. For example, individual parts (e.g. the stimulation electrode) can be repositioned or replaced to continue treatment successfully. In the 33 systematically evaluated publications from a period of ten years (see ch. 9), as well as in the current literature review by Mashaqi et al. (11) no deaths associated with HGNS are reported.

Non-serious adverse events mainly include temporary discomfort associated with neurostimulator implantation, as well as discomfort from electrical stimulation and tongue abrasion. This is also confirmed when used in routine care in patients in the ADHERE registry (76,94,131). In many cases, these complaints subside in the course of acclimation to HGNS therapy or by adjusting the stimulation parameters (19,84,90,114).

As ultima ratio, there is the possibility to resolve adverse events by the explantation of the stimulation system (58–60). This means that, unlike conventional surgical procedures,

treatment with HGNS is reversible because it does not act via anatomical alteration of the upper airway and, accordingly, does not permanently change the anatomy.

Evaluations of an FDA database housing medical device reports in the United States (Manufacturer and User Facility Device Experience (MAUDE) database) indicate a higher proportion of adverse events related to surgical implantation of the neurostimulator (e.g. infection, hematoma, seroma) than in clinical trials, of which infections were the most common reason for explantation overall (60,99). Because infections are a general risk in surgical treatments, this difference may be explained by a divergent assessment of events in terms of their relation to the procedure or to the neurostimulation system (99).

11 Fulfillment of the special requirements of SGB V

In Germany, the billing of services via the statutory health insurance (Gesetzliche Krankenversicherung – GKV) is subject to conditions that are regulated, among other things, in the German Social Law Book V (Sozialgesetzbuch V – SGB V). According to this, services must be "adequate, expedient and economical" and "they must not exceed what is necessary" according to the cost-effectiveness requirements defined in the SGB V (cf. sec. 12 para. 1 SGB V, "Wirtschaftlichkeitsgebot"). The quality and efficacy of the services must correspond to "the generally accepted state of medical knowledge" and follow "medical progress" (sec. 2 para 1 SGB V). In addition, medical treatment must be provided in accordance with "the rules of medical practice" and be "adequate and expedient" (sec. 28 para. 1 SGB V).

For hospital treatment, the provisions of sec. 39 V SGB V and, in addition, sec. 137c SGB V must be considered according to which the so-called "permission principle with prohibition provision" applies to hospital treatment. According to this, in the in-patient treatment coverage of the GKV, examination and treatment methods do not require separate approval and are only excluded from reimbursement if the Federal Joint Committee (G-BA) has negatively evaluated a method and decreed a corresponding guideline. This means that all in-patient examination and treatment methods may in principle be provided at the expense of the GKV without requiring prior authorization.

In the following, the fulfillment of conditions for the billing of HGNS treatment at the expense of the GKV is justified in detail.

11.1 Expedience of treatment

HGNS is an expedient treatment because the available evidence (see ch. 9) reliably suggests efficacy in appropriately selected patients and because the therapy is used successfully by patients on a long-term basis and furthermore HGNS is a safe treatment option, especially in comparison to other surgical procedures.

The efficacy of HGNS is particularly demonstrated in the improvement of patient-relevant outcomes (PRO) (daytime sleepiness, quality of life) and is supported by objective measures (e.g. AHI, ODI) that are suitable for determining the severity of OSA. The systematic literature review shows for the two randomized controlled trials that HGNS led to consistent results with a clinically relevant improvement in quality of life and daytime sleepiness as well as objective reduction in the severity of OSA (35,75). The results of the other studies evaluated also show consistent results for the efficacy of HGNS in OSA (see ch. 9 and Appendix).

As an example, it is referred to the results of the methodologically strongest study by Heiser et al. according to which 76.7% of the participants could be effectively treated with

therapeutic stimulation, which corresponds with clear significance ($p<0.001$) to a difference of plus 47.2% compared to the group with subtherapeutic (sham) stimulation (35). Based on the consistent study results evaluated in this document (see ch. 9), there is sufficient expectation of therapeutic benefit to consider treatment with HGNS as expedient. In their literature review, Mashaqi et al. conclude that HGNS is a very effective alternative therapy for patients intolerant to CPAP (11).

Adjustment of individual stimulation parameters (titration) in the course of a polysomnography (PSG) for individual optimization of treatment is successful in 85% of patients already at the first titration and is completed in the remaining patients in the course of further titrations, if necessary supported by sleep endoscopy (5). The possibility to adjust the stimulation parameters at any time as part of the continuous care of the patients (5) contributes to the long-term expedience of the method (82). The adaptation to the course of the disease and possibly changed conditions is particularly relevant in the treatment of chronic diseases (32).

Study results over an observation period of three (80), four (123) and up to five years (58) show that efficacy is maintained long term. Furthermore, the results in the long-term observation are constant in the period between three and five years and thus do not indicate any "habituation" with regard to the therapeutic effect even with long-term use (58). The intensity of stimulation and sensitivity to stimulation showed no changes over a period of four years with no change in efficacy (significant reduction in AHI) (123). Thus, stimulation of the hypoglossal nerve does not lose efficacy over several years with this method, so that OSA can be successfully treated even in the long term.

Furthermore, the expedience is based on the high safety level of the HGNS, which results from the systematic evaluation of the 33 publications (see ch. 9.2.2). In particular, serious adverse events related to the specific neurostimulation system are rare and can be treated well. Non-serious adverse events, mainly discomfort due to stimulation, are mostly temporary or can be significantly or completely resolved by adjusting the stimulation parameters during titration (84,114). Especially in long-term use, HGNS is well tolerated, which is confirmed by both long-term observations (58,80) as well as registry data from routine care in Germany (94).

The expedience of HGNS results in particular from the fact that CPAP cannot be successfully applied as standard therapy in the respective patients, or that more invasive therapies, which cause a permanent anatomical change in the pharyngeal region with corresponding risks (128) can be avoided.

In addition, the use of HGNS is expedient in that HGNS is expected to be more effective and safer with favorable adherence in appropriate patients compared with conservative therapies, such as treatment with MAD or positional therapy and conventional surgical procedures (see ch. 10).

11.2 Adequate and necessary healthcare provision

If OSA is not effectively treated, patient impairment and adverse health outcomes remain unchanged (30,32). This situation occurs regularly in the treatment with CPAP, because the adherence of patients to this therapy is limited to a relevant extent due to different aspects with a rate of about 50% (22,115). The patients for whom CPAP cannot be successfully applied as the gold standard do not receive adequate treatment and other care is necessary to effectively treat OSA and thus close a therapeutic gap in the treatment of these patients (see ch.10).

If HGNS is applied according to the updated recommendation of the S3 guideline (3) as second-line therapy in selected patients after CPAP failure, it follows that treatment with HGNS is adequate and necessary in these cases, as the patients are otherwise not adequately cared for.

11.3 Economy of treatment

According to sec. 12 para. 1 SGB V, services must be "economical" so that the GKV is allowed to reimburse them. The term "economical" is not defined in sec. 12 para 1 SGB V. There is general consensus that a therapy that is not effective cannot be economical because the costs incurred by the GKV are not justified by a corresponding benefit. Accordingly, effective therapies have a better cost-benefit ratio than non-effective therapies, regardless of their cost.

Therefore, the efficacy of a therapy justifies not only its clinical but also its economic benefit, since only the positive treatment effect can compensate the investment in the treatment – provided that the benefit is not to be questioned by additional expense due to lack of safety. Against this background, the required economic efficiency for the treatment of OSA with hypoglossal nerve stimulation is justified below on the basis of its efficacy and safety.

Accordingly, a therapy can only be economical if it is effective. The proper application of a therapy (adherence) is a basic prerequisite for its efficacy. Therefore, therapy adherence must also be considered to assess the economic efficiency of a method. For the HGNS, an objective assessment of adherence is possible because the usage parameters are recorded by the stimulation systems (45,80). Thus, the cost-effectiveness in terms of adherence can be objectively assessed based on the usage data.

The evaluated studies, including long-term results over five years, document regular use of HGNS with more than five hours of stimulation per night (see ch. 9.2.1.5). Adherence with HGNS is thus significantly higher than with CPAP of an average of 3.3 hours of use per night in a study with more than 2,700 participants (138) (see also ch. 6.4 and 10.1). These results provide the basis for the economical use of HGNS in OSA. In turn, the

efficacy of treatment with appropriate adherence emerges from numerous clinical trials, including two randomized controlled trials (35,75) (see ch. 9.1). Due to the good tolerability of the therapy, also in the long term (see chs. 9.2.2 and 10.3.4), the cost-effectiveness of the method is not expected to be significantly affected by adverse events (see ch. 9.2.2).

Accordingly, HGNS must be considered cost-effective compared with other therapies that cannot be used effectively, since it not only incurs costs in affected patients, but also achieves positive treatment results – based on randomized controlled trials (35,75). Furthermore, successful treatment leads to cost compensation by avoiding or reducing other therapeutic measures and the concomitant diseases associated with OSA (6).

Thus, a better cost-benefit ratio can generally be assumed for HGNS than for ineffective or less effective therapies, as is often the case, for example, with inadequate and thus ineffective use of CPAP (22,115). There are also advantages in comparison with newer surgical therapies, e.g. transoral robotic surgery (TORS) and expansion sphincter pharyngoplasty showed better treatment success with lower complication rates and fewer postoperative readmissions or emergency department presentations for HGNS (139). Thus, HGNS offers clinically and economically relevant advantages over these treatments.

11.4 Current state of medical knowledge

The current state of medical knowledge on a treatment method can result, among other things, from a guideline recommendation or from current scientific publications. For the HGNS method, both a guideline recommendation and numerous scientific publications are available.

A 2020 guideline recommendation is available for the use of HGNS (3). Because the recommendation is based on a systematic literature review, it should be noted that publications published after the literature search was completed may not be included in the respective guideline. The recommendation for HGNS is based on a systematic literature search until 04/30/2019 (3). Accordingly, the recommendation cannot take into account the most recent evidence, e.g. the randomized controlled trial by Heiser et al. (35) or the evidence for more advanced technologies in the form of bilateral stimulation of the hypoglossal nerve (19).

Therefore, the attending physician is required to take new findings from current publications into account, in addition to the guidelines, to treat patients with HGNS based on the current state of medical knowledge. The steadily increasing significance and application of the HGNS therapy since its introduction can be seen as a confirmation that the current medical findings for the treatment of OSA are also relevant in practice.

Qualified framework conditions on site can basically support a treatment as per the current state of medical knowledge. The sleep medicine working group of the DGHNO-

KHC formulated requirements for a suitable treatment center for HGNS (18) which concern both the qualifications and professional experience, as well as the structural resources (18). They are intended to guarantee a high process and outcome quality and to minimize side effects (18). According to the working group sleep medicine of the DGHNO-KHC, the treatment of OSA with the HGNS requires at least the involvement of the specialties sleep medicine and head and neck surgery each with special experience and qualifications in various areas (e.g. PSG, sleep video endoscopy, intraoperative neuromonitoring) (18). Alternatively to head and neck surgery, the method is also performed by other specialties such as neurosurgery, oral and maxillofacial surgery or general surgery with experience in peripheral nerve surgery. The manufacturers of the various neurostimulation systems provide appropriate qualification measures for all users in the form of training courses, implantation training and proctoring. Qualified, multidisciplinary care with the HGNS in accordance with the current state of medical knowledge is typically available at appropriately specialized facilities.

11.5 Application according to the rules of medical art

Sec. 28 (1) SGB V requires that the "treatment of diseases be performed according to the rules of medical art" without further definition. The G-BA's rules of procedure (status August 28, 2021) also do not specify this requirement (74). The verification of whether a treatment is performed according to the rules of medical art must therefore be evaluated on a case-by-case basis.

11.6 Potential of a required treatment alternative

The following chapter explains, based on current regulatory guidance, the extent to which the hypoglossal nerve stimulation method for treating OSA meets the conditions for "potential as a necessary treatment alternative”.

11.6.1 Legal basis

The regulations on the term "potential of a necessary treatment alternative" according to sec. 137c "Evaluation of examination and treatment methods in hospitals" of the SGB V were used as the legal basis. According to this, it is the responsibility of the G-BA to examine, upon application, whether methods are "necessary for adequate, expedient and economical care of the insured persons, taking into account the generally accepted state of medical knowledge" (according to sec. 137c para.1 SGB V).

If the G-BA has neither made a decision according to sec. 137c para.1 SGB V nor adopted a guideline for G-BA confirmation of the benefit ("Erprobung")[8] according to sec. 137e SGB V (this applies to the HGNS), reimbursement in the in-patient sector of the GKV is based on whether the method has the "potential of a necessary treatment alternative" and is applied "according to the rules of medical art" and is thus "particularly medically indicated and necessary" (according to sec. 137c para. 3 cl. 1 SGB V).

According to the G-BA's rules of procedure (Verfahrensordnung, VerfO) (sec. 14 para 3 cl. 1 of chapter 2 of the G-BA's VerfO), as the basis for the evaluation of examination and treatment methods in hospitals in accordance with sec. 137c of the SGB V, as well as the explanatory memorandum to the Act to Strengthen Statutory Health Insurance (GKV-Versorgungsstärkungsgesetz), a potential may arise if:

- a method (treatment alternative) "because of its
  - mechanism of action and
  - of the findings available so far
- is associated with the expectation that
  - other
    - more complex, [or]
    - for the patient more invasive or
    - in certain patients not successfully used

    methods can be substituted, [or]
  - the method has fewer side effects, [or]
  - it means an optimization of the treatment or
  - the method can otherwise provide more effective treatment."[9]

In contrast, a lack of potential arises (according to sec. 14 para 3 cl. 2 of chapter 2 of the G-BA VerfO) "in particular if the G-BA positively proves on the basis of the available evidence that it [the method, authors' note] is harmful or ineffective." This would result in the G-BA excluding the method from reimbursement by the GKV (according to sec. 137c SGB V).

If the G-BA evaluates the "potential of a necessary treatment alternative" in a benefit assessment according to sec. 137c SGB V, the G-BA has to decree a "guideline for confirmation according to sec. 137e". This means that the pending benefit assessment is to be conducted with the aid of a methodologically suitable study. According to sec. 14

[8] G-BA confirmation is conducted with a clinical trial that allows a reliable benefit assessment based on an appropriate study design, typically a randomized controlled trial.
[9] Quoted according to sec. 14 para. 3 cl. 1 of chapter 2 of the G-BA VerfO; the format of the presentation was changed by the authors.

para. 4 of chapter 2 of the G-BA's VerfO, this "potential for confirmation (...) arises in particular when at least such meaningful scientific documentation is available that a study can be planned on this basis that permits an evaluation of the benefit of the method at a sufficiently reliable level of knowledge" (74).

11.6.2 Hypoglossal nerve stimulation offers the potential of a necessary treatment alternative

According to the rules of procedure (VerfO) of the G-BA responsible for the review, whether a method fulfills the conditions for the "potential of a necessary treatment alternative" essentially depends on the available evidence (see previous chapter).

For clarification, it should be pointed out again at this point that in case of HGNS treatment, the evidence should be considered independently of the technology used, because the medical device does not define the method here (see ch. 6.5.3). In its decision of March 5, 2020, the G-BA, as the highest body of self-government in the German healthcare system, qualified "the stimulation of the hypoglossal nerve in this field of application [treatment of OSA, authors' note] as a systematic approach established in-patient care" (49). The G-BA further states that differences in technical design between individual stimulation systems do not lead to a substantial difference with respect to the principle of action and the field of application and therefore do not prevent the "transfer of the available evidence on the benefit, including any risks" (49). This finding of the G-BA is supported by meta-analyses that do not detect significant heterogeneity of results in cross-technology evaluation (97,98).

The systematic review of the 33 systematically searched publications includes two randomized controlled trials, eight prospective single-arm treatment studies, three retrospective studies, several registry evaluations including one non-randomized parallel-arm study, one case series, and three meta-analyses (see chs. 8 and 9). They were conducted in Germany and other countries with comparable medical quality standards (Belgium, the Netherlands, France, the USA, and Australia). Thus, after only ten years of commercial use, the efficacy and safety of HGNS is already comprehensively documented not only by a large number of different studies, but also at a high level of evidence.

The systematically evaluated studies each have comparable inclusion and exclusion criteria for patient selection, similar treatment procedures, and largely consistent outcome parameters. The studies, including long-term data over five years, show similar results in terms of type and extent and, in particular due to the two RCTs, allow the conclusion that the positive treatment results did not occur by chance but are caused by the effect of HGNS. The underlying mechanism of action of HGNS against the pathophysiological background of a neuromuscular dysfunction (32) also suggests that HGNS is an effective therapy for OSA.

Thus, the conditions for the potential of a necessary treatment alternative according to the rules of procedure of the G-BA can be considered fulfilled. This is because the available evidence on efficacy and safety, as well as the underlying mechanism of action, is associated with the expectation that, with the method of HGNS

- more invasive methods can be substituted:

  Conventional surgical procedures are significantly more invasive than HGNS because they permanently alter the patient's anatomy by surgically removing or relocating structures. The invasiveness is also reflected in corresponding risks (see ch. 10.2).

- methods that cannot be used successfully can be substituted:

  Effective use of CPAP as first-line therapy is limited by poor adherence in approximately 50% of cases (22,115). Other non-invasive (conservative) therapies (MAD, positional therapy) are limited in their efficacy to certain patients, sometimes show inconsistent results, and have limitations in adherence (see ch. 10.2).

- the method has fewer side effects:

  Compared with conventional surgical procedures, the risks are minimized with HGNS (128). The potentially lifelong side effects of conventional surgical procedures due to irreversible anatomical changes are entirely avoided, since treatment with HGNS does not alter the patient's anatomy and the neurostimulator can be removed at any time (see ch. 6.5).

- it means an optimization of the treatment:

  In various recent publications, against the background of a multifactorial development of OSA, a more individualized treatment is demanded in order to increase the quality of treatment with an appropriate selection of one or more therapies depending on the findings (140). Here, HGNS offers an important option for an individualized therapy concept (37).

- the method can otherwise provide more effective treatment:

  HGNS demonstrates high, long-term adherence as a basis for effective use of therapy (58), which is also reflected in a high level of patient satisfaction (76,78,94,95). Thus, compared to other methods with limited adherence (CPAP, MAD, positional therapy (see chs. 10.1, 10.2)), HGNS can also achieve improved efficacy in this way.

Furthermore, HGNS has the potential to be a necessary treatment alternative especially because it is intended as a second-line therapy in case of CPAP failure as a first-line therapy (3) and can therefore substitute an unsuccessful treatment or close a therapeutic gap (see ch. 10).

The prerequisite of the plannability of a methodologically suitable study for proof of benefit according to sec. 14 para.4 of chapter 2 of the G-BA VerfO was already fulfilled for the HGNS method prior to the randomized study by Heiser et al. (35) because, in the opinion of the authors, the mentioned multicenter, randomized controlled, double-blinded crossover study is suitable for providing proof of benefit for HGNS for the treatment of OSA at a sufficiently reliable level of knowledge.

Conversely, there is no evidence that the method is harmful or ineffective and should therefore be excluded from care provision. The safety of HGNS has been documented across technologies and up to an observation period of five years (see ch. 9.2.2). The documentation of safety parameters in an international registry with German participation (ADHERE) confirms the safe use of HGNS in routine care.

11.6.3 Aspects of current case law

According to the current opinion of the Federal Social Court (Bundesozialgericht – BSG) (judgment of March 25, 2021 - Ref: B 1 KR 25/20 R, margin no. 40), the use of potential services at the expense of the GKV is "in conflict between innovation and patient protection" and the following requirements are defined in addition (ruling of March 25, 2021 - Ref: B 1 KR 25/20 R, margin no. 40 ff.):

Accordingly, insured persons are entitled to the provision of potential services prior to the decree of a confirmation guideline if the consideration of opportunities and risks is in favor of the potential treatment. This is the case if

1. a serious illness is present in the individual case of treatment, for which
2. according to the respective treatment objective, a standard therapy is not or no longer available (whereby a standard therapy shall not be available if all standard treatments considered are contraindicated or have proven ineffective).

These additional requirements for the provision of services at the expense of GKV are also met by the treatment of OSA with HGNS and justified below.

The severity of the disease with enduring impairment of quality of life is given for OSA due to the particularly common and at the same time limiting symptom of daytime sleepiness with far-reaching effects on the patients' everyday life, e.g. increased risk of accidents, as well as the increased risks for serious comorbidities associated with OSA, e.g. myocardial infarction or stroke. Impaired quality of life has also been documented in numerous studies using validated questionnaires (see ch. 5).

Since HGNS is used as a second-line therapy (3), it is a prerequisite for the indication that no standard treatment, namely CPAP, is available – whereby "available" is concretized by

the BSG as "if all standard treatments considered are contraindicated or have proven ineffective" (judgment of March 25, 2021 - Ref: B 1 KR 25/20 R, para. 42). The indication criterion of "CPAP-intolerance or -inefficacy" fulfills this definition, as patients are only eligible for HGNS if no effective treatment is possible with CPAP (see ch. 6.5.4.1).

Compliance with the relevant regulations of the G-BA's rules of procedure for the acceptance of the potential of a necessary treatment alternative has already been explained in detail in the previous chapter.

11.7 The benefit of hypoglossal nerve stimulation is considered to be proven

With the two randomized controlled trials consistent in type and extent of results (35,75), especially the RCT by Heiser et al. (35) which is characterized by counteracting possible biases by specific measures in the study design (e.g. by increased test strength (power)), a causal relationship between treatment with HGNS and improvement in OSA, including patient-relevant outcomes, can be considered proven from a clinical perspective. The evidence includes patient-relevant outcomes and is based on the second highest level of evidence Ib according to the G-BA (see ch. 9.1) and fulfills the socio-legal requirements of the G-BA according to sec. 11 para. 2 No. 2 and sec. 13 para. 2 of chapter 2 of the G-BA VerfO, since it corresponds to the "Evidence Level I with patient-relevant outcomes" required by the G-BA in the first place.

Together with the results, which are also consistent across the other studies evaluated, the benefit of treatment with HGNS in patients with moderate to severe OSA after CPAP failure ("CPAP-intolerance or -inefficacy", see ch. 6.5.4.1) are considered to be proven. In addition, long-term data demonstrate a sufficient therapy adherence as a prerequisite for the long-term efficacy of HGNS as well as the safe use of the method in the long term (58,80).

In this respect, from the authors' point of view, the question of whether treatment with HGNS offers the "potential of a necessary treatment alternative" does not arise, since the systematically evaluated evidence includes high-quality studies that sufficiently demonstrate the benefit of the method and thus the requirements of "potential" can be considered to be exceeded. This means that the method of hypoglossal nerve stimulation for the treatment of OSA belongs to regular reimbursement in the in-patient sector.

12 Challenges for hypoglossal nerve stimulation

An initial limitation of HGNS was that the neurostimulation systems were not suitable for magnetic resonance imaging (MRI). Through technical advancement, MRI is currently possible with two of the currently available products: i) Inspire-System under certain conditions for the extremities, head, and neck (11), ii) GenioSystem for 1.5 and 3 Tesla whole body MRI examinations (55).

A current challenge is to further increase the proportion of patients who benefit from therapy in order not to expose patients to unnecessary risks. With the help of further studies, the treatment of OSA with HGNS needs to be further developed and optimized for this purpose (112). This concerns, for example, the indication on the basis of additional parameters (141), the use of additional examinations, e.g. manometry (142) and the long-term optimization of the stimulation parameters (143).

Clinical pathways can assist in improving the efficacy and course of treatment with HGNS (126). For challenges in long-term therapy, such as an increase in AHI, persistent symptoms, or inadequate adherence, Whelan and Soose state that guidelines for systematic "best-practice" management are currently being developed (124).

Lastly, studies are expected to determine the extent to which therapy with HGNS can also effectively treat the comorbidities associated with OSA, particularly cardiovascular disease, and reduce mortality.

Currently, various on-going studies for further investigation of the hypoglossal nerve stimulation therapy with the different stimulation technologies for different questions are registered in the worldwide study registry "ClinicalTrials.gov" (144) which will further broaden the evidence base for HGNS in the next years. At this point, only a few studies should be mentioned as examples:

- "THN3" (Targeted Hypoglossal Neurostimulation Study #3) with 138 participants (145),
- "Inspire® Post-Approval Study / Protocol Number 2014-001" with 127 participants (146),
- "CARDIOSA-12" (HGNS on Cardiovascular Outcomes) with 65 participants (111),
- "BETTER SLEEP" (BilatEral Hypoglossal Nerve StimulaTion for TreatmEnt of ObstRuctive SLEEP Apnea With and Without Complete Concentric Collapse) with 42 participants (147),
- "DREAM" (Dual-sided Hypoglossal neRvE stimulAtion for the treatMent of Obstructive Sleep Apnea) with 134 participants (148) and
- "EliSA" (A Post-market Clinical Follow up of the Genio™ System for the Treatment of Obstructive Sleep Apnea in Adults) with 110 participants (149).

12.1 Resilience of the criterion "CPAP-intolerance"

In CPAP, intolerance or non-adherence cannot always be determined by objectively measurable findings. Therefore, in the context of the German healthcare system, the resilience and reproducibility of this indication criterion should be strengthened in individual cases. This could be achieved, for example, by implementing a scheme to standardize the test criteria, the test procedure, and the documentation with the participation of several specialist groups at specialized centers, as has already proven successful for other methods (150,151). In 2020, Fietze et al. published a "Proposal for Standardized Terminology" from a clinical perspective for the five terms "PAP-in-acceptance", “PAP-incompatibility”, "PAP-intolerance", "PAP-failure", and "PAP-discontinuation" (51). In addition, further sharpening of the definition would be desirable. The aim must be to present the respective findings ("intolerance", "inefficacy", "non-adherence", etc.) to uninvolved third parties on the basis of the complete and professionally justified documentation of the testing process and the testing decisions in such a way that the terms used are uniformly defined and the therapy decision is comprehensible.

13 Concluding assessment

There is a great need for effective and safe treatment of obstructive sleep apnea, not only because the disease severely affects many people in Germany in their daily lives and exposes them to serious health risks, but also because society as a whole is affected due to the considerable direct and indirect costs it incurs.

For the treatment of OSA, continuous positive airway pressure (CPAP) therapy is currently considered as the gold standard or first-line therapy. In particular, a lack of adherence to therapy means that about half of patients cannot be successfully treated with CPAP and as a result are continuously affected by the symptoms and health risks of OSA. Affected patients use CPAP inadequately, rendering it ineffective, or discontinue its use completely.

For these patients, in addition to CPAP, various conservative and conventional surgical (second-line) treatment methods are available. The conservative therapies (e.g. positional therapy or treatment with mandibular advancement devices) are restricted to certain patient groups or show limited efficacy. The conventional surgical methods (e.g. uvulopalatopharyngoplasty or maxillo-mandibular advancement) are also only suitable for certain patients and predominantly lack satisfactory efficacy. In addition, the evidence available for these methods, especially on long-term efficacy, is limited in both quantity and quality. Moreover, the conventional surgical methods represent a serious, irreversible intervention that causes permanent anatomical changes in the pharyngeal region. This is associated with corresponding surgical and long-term risks, so that – depending on the respective surgical procedure – a more or less unfavorable cost-benefit ratio results with limited effectiveness.

Due to the numerous limitations of CPAP as well as conservative and conventional surgical treatment alternatives, there is a significant gap in the care of patients with OSA. The method of hypoglossal nerve stimulation makes a significant contribution to closing the existing therapeutic gap in care and therefore represents a valuable addition in the treatment of OSA.

The presentation of the efficacy and safety of the HGNS method is based on extensive and high-quality evidence that fulfills the requirements for a benefit assessment defined in the Federal Joint Committee's (G-BA) rules of procedure (VerfO) (cf. sec.11 para. 2 no. 2 and sec. 13 para. 2 of chapter 2 of the G-BA's VerfO). The evidence includes two randomized controlled trials as well as long-term results with up to five years of observation and numerous single-arm studies, supplemented by data from routine care (registry evaluations).

Based on the systematic search and evaluation of 33 publications, not only are the criteria for the "potential of a necessary treatment alternative" according to sec. 137c SGB V considered to be fulfilled, but the benefit of HGNS for the treatment of OSA is also considered to be sufficiently proven on a high evidence level. This is particularly evident

in the significant and clinically relevant improvement of patient-relevant endpoints (daytime sleepiness, quality of life) in two randomized trials with a therapy-relevant number of study participants relevant for the therapy (total n = 132) (35,75).

Furthermore, the results for the investigated endpoints show a strong consistency across all studies. This means that the improvement in OSA occurred in a comparable manner and to a comparable degree regardless of the particular conditions of the individual study and the technology used and can therefore be reliably expected if properly applied.

HGNS is – unlike conventional surgical procedures – a completely reversible surgical treatment method with a high level of safety. The present systematic literature review shows that serious adverse events related to treatment with HGNS are rare and well treatable. Non-serious adverse events occur mainly in the first weeks after implantation of the neurostimulator and are mainly temporary or resolve after adjustment of the stimulation parameters.

Another important difference and advantage of HGNS compared to conventional surgical procedures is that the adjustment of the stimulation parameters allows the treatment to be adapted to the patient's individual requirements. Thus, HGNS can be adapted to changing conditions at any time, even in the long-term course of OSA. In addition, it is possible to choose between different stimulation technologies (bilateral cyclic, unilateral breath-controlled, unilateral continuous) and thus use the most suitable technology in each individual case.

According to the partial update of the S3 guideline of the DGSM, the method of HGNS for the treatment of OSA has been firmly established in recent years (3). This assessment is confirmed in the updated position paper of the sleep medicine working group of the DGHNO-KHC (18). Based on the present document, the authors expect that the positive recommendation for HGNS for the treatment of OSA, which is already made in the guidelines, will be adapted and enhanced by the responsible societies in the next update due to the evidence that has been added in the meantime.

From a reimbursement perspective, HGNS treatment can be regarded as a method introduced into routine care in Germany. The NUB status 1[10] valid up to and including 2020 was transferred by the German DRG Institute (Institut für das Entgeltsystem im Krankenhaus GmbH (InEK)), which is responsible for the further development of the G-DRG-system, to the regular reimbursement of the aG-DRG-system in 2021 in the form of a newly created supplemental fee (ZE2021-187 "Neurostimulatoren zur Hypoglossusnerv-Stimulation") on the basis of the calculation data from 2019. This means that already in 2019, a sufficient number of cases were treated in several InEK reference hospitals and documented with the associated service and cost data so that InEK could implement a

[10] Rule to bridge reimbursement of new examination and treatment methods (NUB) in the in-patient sector pursuant to sec. 6 para. 2 KHEntgG.

supplemental fee on this data basis and thus anchor the method in the regular reimbursement system.

In summary, the systematic literature review and assessment of the method of HGNS in the context of the German healthcare system leads to the conclusion that the use of HGNS for moderate to severe OSA as second-line therapy after failure of CPAP fulfills the requirements of the SGB V for reimbursement at the expense of the statutory health insurance, as it is expedient and economical, corresponds to the current state of medical knowledge and represents adequate and necessary care.

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Appendix 1: Tabular summary of the studies

In this appendix, in addition to presenting the results of the 33 studies evaluated in chapter 9, each publication is summarized in tables to provide more detailed information about the studies. This is intended to provide a comprehensive overview of the study design on the one hand and the study results on the other. However, this presentation is not suitable for the complete reproduction of all information of the studies. For further details please refer to the respective original publication.

For a better overview, the 33 publications are presented in six groups, each sorted chronologically:

1. 11 publications on different individual studies
2. 7 publications on the STAR trial (Stimulation Therapy for Apnea Reduction)
3. 6 publications on the GPM study (German Post-Market Study)
4. 3 meta-analyses
5. 4 publications on the ADHERE Registry (Adherence and Outcome of Upper Airway Stimulation (UAS) for OSA International Registry)
6. 2 publications on the MAUDE database (Manufacturer and User Facility Device Experience database)

The tabular format of each publication is divided into three parts:

1. General information (incl. conclusion of the abstract)
2. Results on efficacy and further parameters
3. Safety results

Note: In the literature, especially in the USA, it is common practice to describe the patients in a study in terms of their ethnicity (e.g., “Caucasian”, “Hispanic”). This classification is reproduced as a literal quote in the following studies in order not to falsify the statement. We explicitly point out that these are quotations to avoid any possible impression of an evaluation in connection with ethnicities, which could arise, for example, as a result of a translation.

1. Publications on different individual studies

Treating Obstructive Sleep Apnea with Hypoglossal Nerve Stimulation (Eastwood et al., 2011) (41) NCT01186926	
Conclusion: HGNS demonstrated favorable safety, efficacy, and compliance. Participants experienced a significant decrease in OSA severity and OSA-associated symptoms.	
General information about the study (Eastwood et al., 2011)	
Study design / centers (country)	Multicenter, prospective, open-label, single-arm interventional trial; 4 centers: Australia
Inclusion / exclusion criteria	Age 21-70 years; BMI ≤ 40kg/m²; AHI 20-100 events/h and ≥ 15 events/h in non-REM sleep; hypopneas ≥ 80% of the sum of apneas and hypopneas; failure of CPAP treatment despite persistent, supervised attempts; exclusion: prior surgical treatment, combined central or mixed apneas > 5% of all apneas and hypopneas.
Number of patients (p.)	21 p. implanted; 17 p. at 3-month follow-up; 19 p. at 6-month follow-up; exits: 1 p. explantation due to hematoma and infection, 1 p. explantation due to decision for alternative therapy
Patient (p.) characteristics	Age 53.6±9.2 years; 67% men (14/21); BMI 32.7±3.6 kg/m²; systolic blood pressure 131.6±13.2 mmHg; diastolic blood pressure 79.4±9.0 mmHg; neck circumference 41.4±4.9 cm (n=19); "Caucasian" 100%
Procedure / period	Baseline PSG; implantation of HGNS, Apnex Medical System; activation and titration of stimulation approximately 30 days after implantation; outcome measurement (PSG) at 1, 3, and 6 months

Outcomes for efficacy at 6 months compared to baseline (Eastwood et al., 2011) (Baseline values: n=21; 6-month values: n=19)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by 55% from 43.1±17.5 to 19.5±16.7 events/h (p<0.001)
Apnea index	Average decrease from 4.8±7.3 to 1.3±2.2 events/h (p=0.002)
Hypopnea index	Average decrease from 38.3±14.8 to 18.3±16.0 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 16.8±14.4 to 9.1±16.7 events/h (p<0.001)
Total sleep time	No significant change (p=0.88)
Sleep efficiency	Average increase from 76.6%±11.3% to 81.7%±11.6% (p=0.03)
Sleep latency	No significant change (p=0.098)

Continued: Outcomes for efficacy at 6 months compared to baseline (Eastwood et al., 2011) (Baseline values: n=21; 6-month values: n=19)	
Sleep stages (percentage of total sleep time)	• Non-REM sleep 1: average decrease from 27.4%±10.4% to 20.8%±11.5% (p=0.003) • Non-REM sleep 2: No significant change (p=0.62) • Non-REM sleep 3: No significant change (p=0.99) • REM sleep: average increase from 13.5%±5.5% to 17.0%±5.6% (p=0.02)
Sleep fragmentation (by (respiratory) arousal index)	Arousal index: average decrease from 43.8±19.5 to 23.5±15.4 events/h (p<0.001); respiratory arousal index: average decrease from 31.3±20.2 to 11.0±13.8 events/h (p<0.001)
Daytime sleepiness (by ESS)	Average decrease from 12.1±4.7 to 8.1±4.4 points (p<0.001)
Quality of life (by FOSQ, SAQLI)	FOSQ: average increase from 14.4±2.0 to 16.7±2.2 points (p<0.001); SAQLI: average increase from 3.2±1.0 to 4.9±1.3 points (p<0.001)
Sleep quality (by PSQI) (n=18)	Average decrease from 10.1±2.6 to 8.7±3.9 points (p=0.19)
Severity of depressive symptoms (by BDI)	Average decrease from 15.8±9.0 to 9.7±7.6 points (p<0.001)
Duration of use (objective device data) (n=21)	Average of 142±42 nights monitored; average use of 89%±15% of nights for 5.8±1.6 h/night on average

Outcomes for efficacy at 3 months compared to baseline (Eastwood et al., 2011) (Baseline values: n=21; 3-month values: n=17)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by 56% from 43.1±17.5 to 19.0±10.7 events/h (p<0.001)
Apnea index	No significant change (p=0.26)
Hypopnea index	Average decrease from 38.3±14.8 to 16.4±8.8 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 16.8±14.4 to 8.0±7.8 events/h (p<0.001)
Total sleep time	No significant change (p=0.43)
Sleep efficiency	Average increase from 76.65%±11.3% to 82.5%±12.5% (p=0.04)
Sleep latency	No significant change (p=0.14)
Sleep stages (percentage of total sleep time)	• Non-REM sleep 1: average decrease from 27.4%±10.4% to 17.6%±7.5% (p<0.003) • Non-REM sleep 2: No significant change (p=0.96) • Non-REM sleep 3: No significant change (p=0.34) • REM sleep: average increase from 13.5%±5.5% to 18.4%±4.4% (p=0.006)

Continued: Outcomes for efficacy at 3 months compared to baseline (Eastwood et al., 2011) (Baseline values: n=21; 3-month values: n=17)	
Sleep fragmentation (by (respiratory) arousal index)	Arousal index: average decrease from 43.8±19.5 to 23.4±9.6 events/h (p=0.015); respiratory arousal index: average decrease from 31.3±20.2 to 10.5±5.8 events/h (p<0.001)
Daytime sleepiness (by ESS) (baseline: n=21, 3-month n=19)	Average decrease from 12.1±4.7 to 7.9±4.0 points (p<0.001)
Quality of life (by FOSQ, SAQLI) (baseline: n=21, 3-month n=19)	FOSQ: average increase from 14.4±2.0 to 17.0±2.0 points (p<0.001); SAQLI: average increase from 3.2±1.0 to 4.8±1.3 points (p<0.001)
Sleep quality (by PSQI)	Average decrease from 10.1±2.6 to 7.5±3.8 points (p=0.025)
Severity of depressive symptoms (by BDI) (3-month score n=19)	Average decrease from 15.8±9.0 to 8.8±7.5 points (p<0.001)

Outcomes for safety at 6 months (Eastwood et al., 2011) (n=21)	
Parameter	**Result**
Device-related adverse events	Explantation due to hematoma and infection (n=1); explantation due to decision for alternative therapy (n=1); replacement of electrode cuff due to dislodgement (n=1)
Therapy-related adverse events	Tongue abrasion (of short duration and resolved in all cases, most often treated with a plastic tooth guard); at least 1 AE in 67% of p.
Adverse events related to the surgical procedure	Numbness/pain at the incision site; at least 1 AE in 71% of p.
Freedom from serious adverse events related to the device/ therapy/ procedure	After 3 months: 90.2% (19 of 21 p.) After 6 months: 85.2% (18 of 21 p.)

♦ ♦ ♦ ♦

Implanted Upper Airway Stimulation Device for Obstructive Sleep Apnea (Van de Heyning et al., 2012) (42)	
Conclusion: The current study has demonstrated that therapy with upper airway stimulation is safe and efficacious in a select group of patients with moderate to severe OSA who cannot or will not use CPAP as primary treatment.	
General information about the study (Van de Heyning et al., 2012)	
Study design / centers (country)	International, multicenter, prospective, nonrandomized clinical trial in 2 consecutive parts
Inclusion / exclusion criteria	Part 1: BMI < 35kg/m²; AHI ≥ 25 events/h; CPAP failure or intolerance; Part 2: criteria adjusted on the basis of the results from part 1: BMI ≤ 32 kg/m²; AHI 20-50 events/h (1 p. AHI = 60 events/h), no complete concentric collapse at the soft palate
Number of patients (p.)	Part 1: 22 p. implanted, 20 p. at 6-month follow-up; exits: 1 p. due to infection, 1 p. lost to follow-up Part 2: 9 p. implanted, 8 p. at 6-month follow-up; exits: 1 p. inability to activate the tongue with allowed amplitude
Patient (p.) characteristics	Part 1: age 55.7±8.1 years; 100% men (20/20); BMI 29.8±2.7 kg/m² Part 2: age 53.6±11.9 years; 88% men (7/8), BMI 29.8±2.1 kg/m²
Procedure / period	Part 1 (feasibility, safety, predictive factors for therapeutic success) / Part 2 (validation of patient selection): Baseline PSG; implantation of Inspire II system (Inspire Medical Systems, Maple Grove, MN); activation and titration of stimulation 4 weeks after implantation, additional titration at 2 and 4 months if needed; outcome measurement (PSG) at 6 months

Quality of life outcomes at 6 months, study parts 1 and 2 (Van de Heyning et al., 2012) (n=28)	
Parameter	**Result**
Daytime sleepiness (by ESS)	Average decrease from 11.0±5.0 to 7.6±4.3 points (p<0.01)
Quality of life (by FOSQ)	Average increase from 89.1±23.5 to 100.8±16.9 points (p=0.02)

Part 1 of the study: Outcomes for efficacy at 6 months compared to baseline (Van de Heyning et al., 2012) (n=20)	
Parameter	**Result**
Responder rate (≥ 50% reduction of average AHI and AHI < 20 events/h)	6 of 20 p.
Apnea-hypopnea index (AHI) (primary endpoint)	Responders: average decrease from 26.1±4.5 to 7.7±4.1 events/h (p<0.01) Non-responders: no significant change (p=0.40)
Apnea-hypopnea index (AHI) in REM sleep	Responders: average decrease from 38.2±9.5 to 11.1±9.3 events/h (p<0.01) Non-responders: no significant change (p=0.82)
Apnea-hypopnea Index (AHI) in non-REM sleep	Responders: average decrease from 24.2±4.1 to 7.0±3.8 events/h (p<0.01) Non-responders: no significant change (p=0.29)
Apnea index	Responders: average decrease from 15.3±8.3 to 2.5±1.4 events/h (p=0.02) Non-responders: no significant change (p=0.22)
Hypopnea index	Responders: no significant change (p=0.19) Non-responders: no significant change (p=0.27)
Oxygen desaturation index (ODI) (primary endpoint)	Responders: average decrease from 14.5±7.2 to 6.7±4.3 events/h (p<0.05) Non-responders: no significant change (p=0.10)
Total sleep time	Responders: no significant change (p=0.80) Non-responders: no significant change (p=0.16)
Sleep efficiency	Responders: no significant change (p=0.35) Non-responders: no significant change (p=0.34)
Sleep stages (percentages)	Responders: no significant change: N1 sleep (p=0.15), N2 sleep (p=0.15), N3 sleep (p=0.58), REM sleep (p=0.70) Non-responders: no significant change: N1 sleep (p=0.24), N2 sleep (p=0.15), N3 sleep (p=0.78), REM sleep (p=0.74)

Part 1 of the study: predictors of therapy success related to baseline values (Van de Heyning et al., 2012)	
Apnea-hypopnea index (AHI) and Body Mass Index (BMI)	Association with treatment success: AHI ≤ 50 events/h combined with BMI ≤ 32 kg/m² (p=0.01)
Upper airway collapse patterns on sleep endoscopy (n=7)	No complete concentric collapse at the soft palate (CCC): all responders (n=3); complete concentric collapse at the soft palate (CCC): all non-responders (n=4)
Daytime sleepiness (by ESS)	No significant association
Quality of life (by FOSQ)	No significant association

Part 2 of the study: Outcomes for efficacy after 6 months compared to baseline (Van de Heyning et al., 2012) (n=8)	
Parameter	**Result**
Responder rate (≥ 50% reduction of average AHI and AHI < 20 events/h)	7 of 8 p.
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease from 38.9±9.8 to 10.0±11.0 events/h (p<0.01)
Apnea-hypopnea index in REM sleep	Average decrease 28.2±17.7 to 9.0±9.4 events/h (p=0.01)
Apnea-hypopnea index in non-REM sleep	Average decrease 39.6±10.8 to 10.0±12.1 events/h (p<0.01)
Apnea index	Average decrease from 22.7±8.2 to 6.4±9.7 events/h (p<0.01)
Hypopnea index	Average decrease from 22.7±8.2 to 6.4±9.7 events/h (p<0.01)
Oxygen desaturation index (ODI) (primary endpoint)	Average decrease 32.1±15.1 to 9.5±10.2 events/h (p<0.01)
Total sleep time	No significant change (p=0.53)
Sleep efficiency	No significant change (p=0.66)
Sleep stages (percentages)	No significant change: N1 sleep (p=0.24), N2 sleep (p=0.10), N3 sleep (p=0.58), REM sleep (p=0.59)

Outcomes for safety at 6 months, study parts 1 and 2 (Van de Heyning et al., 2012) (n=28)	
Parameter	**Result**
Device-related serious adverse events	Pain and swelling at neck incision site immediately post implantation (n=1); delayed infection post implantation followed by explantation (n=1)
Non-serious adverse events	Pain and stiffness postoperatively (n=7); sore throat (n=4); cutaneous stitch abscess (n=1); local swelling (n=1); fever (n=1); lack of tongue response to stimulation (n=1); all AEs resolved without intervention

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Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes (Kezirian et al., 2014) (47) Australia: NCT01186926, USA: NCT012114444	
Conclusion: Hypoglossal nerve stimulation demonstrated favorable safety, feasibility and efficacy.	
General information about the study (Kezirian et al., 2014)	
Study design / centers (country)	International, multicenter, prospective, open-label, single-arm clinical trial; 8 centers: Australia, USA
Inclusion / exclusion criteria	Age 21-70 years; BMI ≤ 40kg/m² (Australia) or ≤ 37kg/m² (USA); AHI 20-100 events/h; 15 events/h in REM sleep; hypopneas ≥ 80% of sum of apneas and hypopneas; exclusion: surgical history, combined central or mixed apneas > 5%
Number of patients (p.)	32 p. implanted; 31 p. evaluated; exits: 4 p. explanted: 1 p. before activation of stimulation, 2 p. due to lack of sufficient objective and subjective effectiveness, 1 p. due to infection
Patient (p.) characteristics	Age 52.4±9.4 years; 35% women (11/31 p.); BMI 32.4±3.6kg/m²; "non-Hispanic Caucasian" 90% (28/31 p.), 1 p. each "Hispanic Caucasian", "Black/African American", "multiracial"
Procedure / period	Baseline PSG; implantation of the HGNS system (Apnex Medical, St. Paul, MN, USA); activation and titration of stimulation approximately 1 month after implantation; outcome measurement (PSG) at 3, 6, and 12 months

Outcomes for efficacy at 6 months compared to baseline (Kezirian et al., 2014) Intention-to-treat analysis; use of most recent available data carried forward for 2 p. (n=31)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease from 45.4±17.5 to 20.8±17.6 events/h (p<0.001)
Apnea index	Average decrease from 4.6±6.3 to 1.5±2.2 events/h (p<0.001)
Hypopnea index	Average decrease from 40.8±15.3 to 19.4±16.6 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 20.9±17.3 to 10.7±17.1 events/h (p<0.001)
Sleep fragmentation (by (respiratory) arousal index)	Arousal index: average decrease from 44.3±17.7 to 24.4±13.2 events/h (p<0.001); respiratory arousal index: average decrease from 31.4±18.4 to 11.9±11.9 events/h (p<0.001)
Total sleep time	No significant change
Sleep efficiency	Average increase from 77.2%±12.6% to 82.8%±10.9% (p<0.05, but >0.001)

Continued: Outcomes for efficacy at 6 months compared to baseline (Kezirian et al., 2014) Intention-to-treat analysis; use of most recent available data carried forward for 2 p. (n=31)	
Sleep stages (percentages)	• Non-REM sleep 1: average increase from 29.3%±11.2% to 20.5%±10.2% (p<0.001) • Non-REM sleep 2: no significant change • Non-REM sleep 3: no significant change • REM sleep: average increase from 12.6%±6.5% to 16.1%±5.7% (p<0.05, but <0.001)
Sleep fragmentation (by arousal index)	Average decrease from 44.3±17.7 to 24.4±13.2 events/h (p<0.001)
Daytime sleepiness (by ESS)	Average decrease from 12.1±4.6 to 8.3±3.6 points (p<0.001)
Quality of life (by FOSQ (primary endpoint), SAQLI)	FOSQ: average increase from 14.2±2.0 to 16.8±2.4 points (p<0.001); SAQLI: average increase from 3.1±1.1 to 4.8±1.4 points (p<0.001)
Restriction of sleep quality (by PSQI)	No significant change
Severity of depressive symptoms (by BDI)	Average decrease from 15.7±9.0 to 8.5±7.8 points (p<0.001)

Outcomes for efficacy at 12 months compared to baseline (Kezirian et al., 2014) Intention-to-treat analysis; use of most recent available data carried forward for 3 p. (n=31). No significant changes compared to 6-month values (p>0.10; ODI: p=0.09; quality-of-life-related parameters: p>0.60)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease from 45.4±17.5 to 25.3±20.6 events/h (p<0.001)
Apnea index	Average decrease from 4.6±6.3 to 3.2±5.9 events/h (p<0.05, but >0.001)
Hypopnea index	Average decrease from 40.8±15.3 to 22.1±17.9 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 20.9±17.3 to 15.7±19.6 events/h (p<0.001)
Sleep fragmentation (by (respiratory) Arousal index)	Arousal index: average decrease from 44.3±17.7 to 27.5±13.4 events/h (p<0.001); Respiratory arousal index: average decrease from 31.4±18.4 to 14.4±12.4 events/h (p<0.001)
Total sleep time	No significant change
Sleep efficiency	Average increase from 77.2%±12.6% to 82.6%±10.2% (p<0.05, but >0.001)
Sleep stages (percentages)	• Non-REM sleep 1: average decrease from 29.3%±11.2% to 21.8%±10.3% (p<0.001) • Non-REM sleep 2: no significant change • Non-REM sleep 3: no significant change • REM sleep: average increase from 12.6%±6.5% to 16.4%±5.0% (p<0.05, but <0.001)

Continued: Outcomes for efficacy at 12 months compared to baseline (Kezirian et al., 2014) Intention-to-treat analysis; use of most recent available data carried forward for 3 p. (n=31) No significant changes compared to 6-month values (p>0.10; ODI: p=0.09; quality-of-life-related parameters: p>0.60)	
Daytime sleepiness (by ESS)	Average decrease from 12.1±4.6 to 7.9±3.8 points (p<0.001)
Quality of life (by FOSQ (primary endpoint), SAQLI)	FOSQ: average increase from 14.2±2.0 to 17.0±2.4 points (p<0.001); SAQLI: average increase from 3.1±1.1 to 4.9±1.4 points (p<0.001)
Restriction of sleep quality (by PSQI)	Average decrease from 9.9±3.2 to 7.8±4.3 points (p<0.05, but >0.001)
Severity of depressive symptoms (by BDI)	Average decrease from 15.7±9.0 to 9.1±8.2 points (p<0.001)
Responder rate (by AHI)	• ≥ 50% reduction in AHI to <20 events/h: 55% (17/31 p.) • ≥ 50% reduction in AHI to <15 events/h: 48% (15/31 p.) • ≥ 50% reduction in AHI to <15 events/h: 6% (2/31 p.)
Duration of use (objective device data)	On average in 86%±16% of nights (42%-100%) for 5.4±1.4 h/night (2.7-8.4 h/night)

Outcomes for safety at 12 months (Kezirian et al., 2014) (n=31)	
Parameter	**Result**
Device-related serious adverse events	4 explants: Patient request before activation (n=1), lack of sufficient objective and subjective effectiveness (n=2), infection (n=1); 2 dislodgements of the stimulation lead cuff within 2 weeks after implantation with surgical replacement without sequelae
Adverse events related to the surgical procedure	Most common AE: numbness/pain at incision sites: 35% (11/31 p.), persistent after 12 months: 26% (8/31 p.); readmission of 1 p. due to psychological disturbance related to postoperative pain medication; at least 1 AE in 71% of p. (22/31 p.)
Therapy-related adverse events	Most frequent AE: tongue abrasion: 55% of p. (17/31 p.) (of short duration and self-limited, successfully treated by a plastic dental guard); tongue soreness persistent after 12 months: 10% of p. (3/31 p.); at least 1 AE in 32% of p. (10/31 p.); SAE in 10% of p. (3/31 p.)
Adverse events after 12 months	Numbness/pain at incision sites: 26% (8/31 p.) Tongue soreness: 10% (3/31 p.)
Freedom from adverse events related to the device/therapy/procedure	71% (22/31 p.)

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Targeted Hypoglossal Nerve Stimulation for the Treatment of Obstructive Sleep Apnea: Six-Month Results (Friedman et al., 2016) (90) NCT01796925	
Conclusion: This feasibility study suggests that THN therapy is likely to be safe and effective in selected patients.	
General information about the study (Friedman et al., 2016)	
Study design / centers (country)	International, multicenter, prospective, open-label, single-arm cohort study; 7 centers: USA, Germany, Belgium
Inclusion/ exclusion criteria	BMI ≤ 37kg/m²; AHI ≥ 20 events/h; CPAP intolerance (not used for ≥ 4 h/night for ≥ 5 days/week for the preceding 4 weeks); exclusion: ≥ 10% central sleep apnea, positional OSA
Number of patients (p.)	46 p. implanted; 43 p. at 6-month follow-up; exits: 1 p. consent withdrawn; 1 p. withdrawn by physician; 1 p. missed 6-month follow-up
Patient (p.) characteristics	Age 54.9±11.1 years; 93% men (43/46); BMI 30.8±3.7kg/m²
Procedure/ period	Baseline PSG, implantation of ImThera aura6000 system; activation and titration of stimulation 3-4 weeks after implantation; outcome measurement (PSG) after 6 months

Outcomes for efficacy at 6 months compared to baseline (Friedman et al., 2016) (n=43)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease by 9.5±20.6 from 34.9±22.5 to 25.4±23.1 events/h (p=0.004)
AHI responder rate (≥ 50% reduction in AHI and AHI < 20 events/h)	34.9% of p. (15/43 p.)
Oxygen desaturation index (ODI) (primary endpoint)	Average decrease by 8.8±20.0 from 32.4±22.3 to 23.6±22.3 events/h (p=0.006)
ODI responder rate (> 50% reduction of the ODI)	39.5% of p. (17/43 p.)
Sleep fragmentation (by arousal index) (secondary endpoint)	Average decrease by 11.1±19.0 from 42.7±19.4 to 31.6±20.3 events/h (p<0.001)
Daytime sleepiness (by ESS) (secondary endpoint)	Average decrease by 3.8±4.7 from 12.0±4.8 to 8.3±4.4 points (p<0.001)
Quality of life (by SAQLI) (secondary endpoint)	Average increase by 0.4±1.1 from 4.3±1.0 to 4.7±1.2 points (p=0.019)

Outcomes for efficacy: predictors of treatment success (Friedman et al., 2016)	
Parameter	**Result**
Positive predictors (baseline values)	Combination of AHI < 65 events/h, apnea index ≤ 30 events/h, BMI < 35 kg/m², > 10% drop in oxygen saturation < 15 events/h

Outcomes for safety at 6 months (Friedman et al., 2016) (n=46)	
Parameter	**Result**
Short-term serious adverse events (occurrence ≤ 30 days after implantation)	Total of 6 AE in 6 p. (of which 5 AE related to the device or surgical procedure): hematoma (n=1), pain (n=1), bleeding (n=1), no stimulation (n=1), other AE (n=2)
Long-term serious adverse events (occurrence > 30 days after implantation)	Total of 6 AE in 5 p. (of which 3 AE related to the device or surgical procedure): pain (n=2), device migration (n=1), other AE (n=3).
Short-term, transient, non-serious adverse events (occurrence ≤ 30 days after implantation)	Total of 31 AE in 20 p. (of which 29 AE related to the device or surgical procedure): pain (n=7), paresis (n=5), paresthesia (n=5), infection (n=4), hematoma (n=1), other AE (n=1), anesthesia complication (n=1)
Long-term, non-serious adverse events (occurrence > 30 days after implantation)	Total of 31 AE in 20 p. (of which 29 AE related to the device or surgical procedure): pain (n=12), hematoma (n=2), paresthesia (n=1), other AE (n=16)

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Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience (Heiser et al., 2017a) (86)	
Conclusion: In the setting of a tertiary referral center, patients with moderate to severe OSA and incompliance to CPAP therapy reduced OSA severity and improved subjective daytime sleepiness after receiving upper airway stimulation therapy. Patient maintained high adherence of therapy use after 12 months. It is encouraging that the upper airway stimulation has been shown to be successfully implemented in the routine clinical management of OSA outside of a clinical trial setting.	
General information about the study (Heiser et al., 2017a)	
Study design / centers (country)	Single-center, prospective, single-arm clinical trial; Germany
Inclusion / exclusion criteria	AHI >15 and <65 events/h; central apnea index < 25%; nonadherence to CPAP treatment; exclusion: complete concentric collapse of the soft palate, BMI > 35 kg/m²
Number of patients (p.)	31 p. implanted and evaluated
Patient (p.) characteristics	Age 59.6±10.9 years; 97% men (30/31); BMI 28.8±3.1kg/m²; average time between diagnosis and implantation 33.6±45.1 months
Procedure / period	Baseline PSG; implantation of the Inspire II Upper Airway Stimulation System (Inspire Medical Systems, Maple Grove, MN, USA); activation of stimulation at 1 month; titration of stimulation and outcome measurement (PSG) at 2 and 3 months; outcome measurement (home sleep polygraphy) at 6 and 12 months

Outcomes for efficacy at 2 months compared to baseline (Heiser et al., 2017a) (n=31)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 32.9±11.2 to 11.5±14.1 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 30.7±14.0 to 13.7±12.2 events/h (p<0.001)
Mean oxygen saturation	Average increase from 92.3%±2.4% to 93.8%±2.0% (p<0.001)
Minimum oxygen saturation	Average increase from 74.1%±11.4% to 83.8%±5.2% (p<0.001)
Daytime sleepiness (by ESS)	Average decrease from 12.6±5.6 to 8.6±5.0 points (p<0,001)
Duration of use	Average 7.0±1.5 h/night

Outcomes for efficacy at 3 months compared to baseline (Heiser et al., 2017a) (n=31) No significant changes compared to 2-month values (p=0.076 (ESS) to p=0.995 (AHI))	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 32.9±11.2 to 10.3±13.0 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 30.7±14.0 to 13.8±13.8 events/h (p<0.001)
Mean oxygen saturation	Average increase from 92.3%±2.4% to 93.7%±2.0% (p=0.001)
Minimum oxygen saturation	Average increase from 74.1%±11.4% to 84.5%±5.6% (p<0.001)
Daytime sleepiness (by ESS)	Average decrease from 12.6±5.6 to 6.8±4.8 points (p<0.001)
Duration of use	6.9±2.3 h/night on average

Outcomes for efficacy at 6 months compared to baseline (Heiser et al., 2017a) (n=31) No significant changes compared to 3-month values (p=0.062 (mean oxygen saturation) to p=0.770 (ODI)), except for minimum oxygen saturation: decrease from 84.5%±5.6% to 79.1%±11.1% (p=0.017)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 32.9±11.2 to 7.6±5.3 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 30.7±14.0 to 11.7±8.8 events/h (p<0.001)
Mean oxygen saturation	No significant change (p=0.762)
Minimum oxygen saturation	No significant change (p=0.108)
Daytime sleepiness (by ESS)	Average decrease from 12.6±5.6 to 5.9±4.8 points (p=0.001)
Duration of use	6.0±2.2 h/night on average

Outcomes for efficacy at 12 months compared to baseline (Heiser et al., 2017a) (n=31) No significant changes compared to 6-month values (p=0.071 (minimum oxygen saturation) to p=0.564 (ODI))	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 32.9±11.2 to 7.1±5.9 events/h (p<0.001).
Oxygen desaturation index (ODI)	Average decrease from 30.7±14.0 to 9.9±8.0 events/h (p=004).
Mean oxygen saturation	No significant change (p=0.307)
Minimum oxygen saturation	No significant change (p=0.151)
Daytime sleepiness (by ESS)	Average decrease from 12.6±5.6 to 5.9±5.2 points (p=0.006)
Duration of use	6.6±2.7 h/night on average

Outcomes for safety at 12 months (Heiser et al., 2017a) (n=31)	
Parameter	**Result**
Adverse events	Rupture of a venous vessel during the cervical tunneling: 2 p., 1 of which required further cervical incision

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Upper Airway Stimulation for Treatment of Obstructive Sleep Apnea: An Evaluation and Comparison of Outcomes at Two Academic Centers (Huntley et al., 2017) (88)	
Conclusion: UAS appears to provide a viable alternative to continuous positive airway pressure, producing improvement in both polysomnographic and quality-of-life measures. Results are reproducible at high-volume centers.	
General information about the study (Huntley et al., 2017)	
Study design / centers (country)	Multicenter, retrospective cohort study; 2 centers: USA
Inclusion / exclusion criteria	Moderate to severe OSA; inadequate CPAP adherence; exclusion: complete concentric collapse at the level of the soft palate
Number of patients (p.)	A total of 97 p. implanted and evaluated (1st center 48 p., 2nd center 49 p.)
Patient (p.) characteristics	1st center: age 60.88±11.12 years; men 30/48; BMI 29.29±3.72 kg/m²; 2nd center: age 62.84±10.81 years; men 30/49; BMI 27.74±3.66 kg/m²
Procedure / period	Baseline PSG; implantation of Inspire hypoglossal nerve stimulator (Inspire Medical Systems, Minneapolis, Minnesota, USA); activation of stimulation 4 weeks after implantation; titration of stimulation and outcome measurement (PSG) after 2 months

Outcomes for efficacy at 2 months compared to baseline (Huntley et al., 2017) (n=48 in the 1st center; n=49 in the 2nd center)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	1st center: Average decrease from 35.88±20.82 to 6.34±11.50 events/h (p<0.001) 2nd center: Average decrease from 35.29±15.33 to 6.28±6.10 events/h (p<0.001) No significant difference between centers (baseline p=0.280, 2-months p=0188, percentage p. with: AHI < 15 events/h p=0.464, AHI < 10 events/h p=0.537, AHI < 5 events/h p=0.433)
Oxygen nadir	1st center: Average increase from 80.96%±7.90% to 88.04%±3.40% (p<0.001) 2nd center: Average increase from 79.58%±7.18% to 84.35%±4.74% events/h (p<0.001) Baseline: no significant difference between centers (p=0.801), after 2 months greater increase in 1st center (p=0.025)
Daytime sleepiness (by ESS)	1st center: Average decrease from 11.09±3.77 to 5.77±3.35 points (p<0.001) 2nd center: Average decrease from 10.94±4.89 to 6.60±4.51 (p<0.001) No significant difference between centers (baseline p=0.181, 2-month p=0.120)
Surgical success (≥ 50% reduction in AHI and AHI < 20 events/h) (percentage of p.)	No significant difference between centers: p=0.643
Duration of use (objective device data)	1st center: At a mean of 90.39±62.69 days since surgery: average use of 48.52±14.49 h/week, and use > 40 h/week: 77.70% of p.; at a mean of 258.06±129.23 days since surgery: average use of 43.75±11.60 h/week, and use > 40 h/week: 63.40% of p. 2nd center: At a mean of 85.23±38.02 days since surgery: average use of 46.60±14.02 h/week, and use > 40 h/week: 76.10% of p.; at a mean of 343.49±215.63 days since surgery: average use of 48.00±10.24 h/week, and use > 40 h/week: 78.80% of p.

Outcomes for safety (Huntley et al., 2017) (n=48 at 1st center; n=49 at 2nd center)	
Parameter	**Result**
Device-related adverse events	1st center: Headache (n=3), tongue discomfort (n=3), dysarthria (n=2), multiple awakenings (n=1) 2nd center: Dry mouth (n=4), headache (n=3), incisional discomfort (n=2), tongue abrasion (n=1), awakening by activated device (n=1)
Adverse events related to the surgical procedure	1st center: Temporary hypoglossal nerve paresis (n=1), temporary minor mandibular nerve paresis (n=2), temporary dysarthria (n=1), explantation at patient's request due to perceived lack of symptomatic improvement (n=1) 2nd center: Seroma (n=2), temporary marginal paresis of the mandibular nerve (n=1)

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Hypoglossal Nerve Stimulator Implantation in a Non-Academic Setting: Two-Year Result (Weeks et al., 2018) (91)	
Conclusion: Patients who elected to receive UAS implant surgery at a non-academic hospital and followed at a sleep clinic showed significant reduction in OSA severity with strong adherence to treatment. These results supported that UAS as a valid treatment option for OSA can be successfully implemented in the non-academic hospital and clinic settings.	
General information about the study (Weeks et al., 2018)	
Study design / centers (country)	Single-center, retrospective case series; USA
Inclusion / exclusion criteria	Moderate to severe OSA; BMI ≤ 32kg/m²; no complete concentric collapse at the level of the soft palate; patients not able to adhere to PAP therapy
Number of patients (p.)	22 p. implanted, 21 p. evaluated; exclusion: 1 p. without titration
Patient (p.) characteristics	Age 63.2±11.1 years; male/female 17/5; BMI 28.9±5.0 kg/m²; "White" 19 p., "Hispanic" 2 p., "Other" 1 p.
Procedure / period	Baseline PSG; implantation of the Inspire UAS system (Inspire Medical Systems, Minneapolis, MN, USA); activation of stimulation 1 month after implantation; titration of stimulation after 2 months; outcome measurement (PSG) at a mean of 95.0±28.5 (56-141) days after implantation

Outcomes for efficacy compared to baseline (Weeks et al., 2018) (n=21)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 35.9±19.1 to 16.0±10.4 events/h (p<0.001), and after optimization of programming settings to 1.2±1.8 events/h (p<0.001), respectively with AHI < 5 events/h: 90% of p.; comparable results in p. with (n=10) and without (n=11) previous OSA surgery
Minimum oxygen saturation	Average increase from 81%±8% to 91%±3% (p=0.001)
Daytime sleepiness (by ESS) (n=18)	Average decrease from 10.9±4.8 to 6.7±5.3 points; ESS < 10 points: 13 p.
Duration of use (objective device data) (n=18)	7.0±1.9 h/night on average

Outcomes for safety (Weeks et al., 2018) (n=22)	
Parameter	**Result**
Adverse events	Seroma (n=1)

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Upper Airway Stimulation Therapy and Sleep Architecture in Patients With Obstructive Sleep Apnea (Bohorquez et al., 2020) (87)	
Conclusion: There was significant improvement across several sleep architecture parameters among patients who responded successfully to UAS implantation.	
General information about the study (Bohorquez et al., 2020).	
Study design / centers (country)	Single-center, retrospective chart review; USA
Inclusion / exclusion criteria	Moderate to severe OSA; failed CPAP trial; exclusion: complete concentric retropalatal collapse (Definition of treatment success according to Sher: reduction in AHI by at least 50% and an absolute AHI below 20 events/h) (113)) during postoperative PSG
Number of patients (p.)	40 p. identified; 35 p. evaluated; exclusion: 2 p. due to incomplete data, 3 p. due to titration without treatment success
Patient (p.) characteristics	Age 63.4±12.2 years; men/women: 33/4; BMI 30.0±0.56 kg/m²
Procedure / period	Baseline PSG; implantation of the Inspire II system (Inspire Medical Systems, Inc.); activation of stimulation 1 month after implantation; titration of stimulation and outcome measurement (PSG) at 2 months

Outcomes for efficacy at 2 months compared to baseline (Bohorquez et al., 2020) (n=35)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 36.8±2.4 to 2.6±0.66 events/h
Nadir oxyhemoglobin saturation	Average increase from 76.3%±2.6% to 91.3%±0.41%
Peripheral capillary oxygen saturation (SpO_2) < 88% (duration)	Average decrease from 13.6±3.3 to 0.05±0.02 minutes
Time with SpO_2 < 88% (percentage of total sleep time)	Average decrease from 8.1%±2.9% to 0.92%±0.75%
Time in success (Sher criteria are met) during the PSG Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	226.3±101.3 minutes on average
Duration of use	On average: 49.1±12.4 h/week, approx. 7 h/night
BMI	No significant change (p=0.888)
Total sleep time (TST)	No significant change (p=0.092)
Sleep stages (duration and percentage of total sleep time)	• Non-REM sleep 1: duration: no significant change (p=0.364), percentage: decrease from 16.7%±2.1% to 10.1%±1.6% (p=0.023) • Non-REM sleep 2: duration: average increase from 148.0±12.4 to 185.5±10.4 minutes (p=0.030), percentage: no significant change (p=0.902) • Non-REM sleep 3: average increase from 21.9±5.0 to 57.0±11.1 minutes (p=0.013), percentage: no significant change (p=0.070) • REM sleep: no significant change (p=0.218), percentage: no significant change (p=0.963)
Sleep latency (duration)	No significant change (p=0.541)
REM latency (duration)	No significant change (p=0.489)
Wake after sleep onset (duration)	No significant change (p=0.052)
Sleep fragmentation (by arousal index)	Average decrease from 38.8±4.0 to 30.3±4.0 events/h (p=0.050)
Sleep efficiency	No significant change (p=0.459)

Outcomes for safety (Bohorquez et al., 2020) (n=35)	
Parameter	**Result**
Serious adverse events	None

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Bilateral hypoglossal nerve stimulation for treatment of adult obstructive sleep apnea (Eastwood et al., 2020) (19) (BLAST OSA Study) NCT03048604	
Conclusion: Bilateral HNS using the Genio™ system reduces OSA severity and improves quality of life without device-related complications. The results are comparable with previously published HNS systems despite minimal implanted components and a simple stimulation algorithm.	
General information about the study (Eastwood et al., 2020)	
Study design / centers (country)	International, multicenter, prospective, open-label, nonrandomized, single-arm treatment study; 7 centers: France, Australia.
Inclusion / exclusion criteria	Age 21-75 years; BMI ≤ 32 kg/m²; AHI 20-60 events/h; combined central and mixed AHI events < 10/h; no positional OSA (non-supine AHI < 10 events/h and supine AHI ≥ 2 times non-supine AHI); no complete concentric collapse (CCC) of the soft palate; PAP therapy not tolerated/accepted; MAD intolerance (France only)
Number of patients (p.)	27 p. implanted and at 6-week follow-up; 22 p. at 6-month follow-up; exits: 2 p. due to infections; 1 p. unrelated to the study; 1 p. after implantation despite only limited intraoperative response to stimulation; 1 p. unavailable at 6 months
Patient (p.) characteristics	Age 55.9±12.0 years; 63% men (17/27); BMI 27.4±3.0 kg/m²; systolic blood pressure 130.4±17.5 mmHg; diastolic blood pressure 78±6.6 mmHg; neck circumference 39.0±4.2 cm (n=24); “Caucasian” 88.9% (24/27), “Hispanic” 11.1% (3/27)
Procedure / period	Baseline PSG; implantation of the Genio system (Nyxoah SA, Mont-Saint-Guibert, Belgium) for bilateral HGNS; activation of stimulation 4-6 weeks after implantation; titration of stimulation at 2, 3, and 4 months; outcome measurement (PSG) at 6 months

Outcomes for efficacy at 6 months compared to baseline (Eastwood et al., 2020) Modified intention-to-treat analysis with exclusion of 5 patients (n=22)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease by 10.8 (CI: 14.6;7.0) from 23.7±12.2 to 12.9±10.1 events/h (p<0.0001) or by 47.3% (median 48.6%); remaining AHI: < 15 events/h (n=11), < 10 events/h (n=4), < 5 events/h (n=3)
Apnea index	Average decrease by 4.8 (CI: 9.2;0.4) from 10.1±10.2 to 5.6±8.4 events/h (p=0.0334)
Hypopnea index	Average decrease by 4.9 (CI: 8.1;1.7) from 12.5±8.9 to 7.6±6.2 events/h (p=0.0049)

Continued: Outcomes for efficacy at 6 months compared to baseline (Eastwood et al., 2020) Modified intention-to-treat analysis with exclusion of 5 patients (n=22)	
Oxygen desaturation index (ODI) (secondary endpoint)	Average decrease by 9.3 (CI: 13.1;5.5) from 19.1±11.2 to 9.8±6.9 events/h (p<0.0001) or by 43.3% (median 47.2%)
Oxygen saturation < 90% (percentage of sleep time)	Average decrease by 2.9% (CI: 4.6;1.3) from 5.0%±6.0% to 2.1%±3.0% (p=0.0015)
Sleep efficiency (percentage of time spent sleeping to time spent in bed).	Average increase by 3.2% (CI: 0.01;6.4) from 84.0%±10.8% to 87.3%±8.9% (p=0.0494)
Sleep stages (percentage of sleep time)	• Non-REM sleep 1: average decrease by 5.0% (CI: 8.3;1.7) from 13.1%±7.9% to 8.2%±4.0% (p=0.0053); • Non-REM sleep 2: average increase by 6.7% (CI: 2.2;11.3) from 60.9%±8.7% to 67.6%±9.5% (p=0.0058); • Non-REM sleep 3: average decrease by 4.7% (CI: 6.6;2.7) from 8.2%±6.9% to 3.5%±4.3% (p<0.001); • REM sleep: no significant change (p=0.0782)
Sleep fragmentation (by Arousal index)	Average decrease by 12.7 (CI: 16.6;8.9) from 28.7±11.5 to 16.0±8.0 events/h (p<0.0001)
Daytime sleepiness (by ESS) (baseline: n=21)	Average decrease by 3.0 (CI: 5.7;0.8) from 11.0±5.3 to 8.0±5.4 points (p=0.0113)
Quality of life (by FOSQ-10)	Average increase by 1.9 (CI: 0.4;3.4) from 15.3±3.3 to 17.2±3.0 points (p=0.0157)
Responder rate (≥ 50% reduction in mean AHI and AHI < 20 events/h)	50.0% (11 of 22 p.)
Heavy, disturbing snoring (reported by partner)	Average decrease from 96% to 35
Duration of use (patient reported)	> 5 nights/week: 91% of p.; > 5 h/night: 77% of p.

Outcomes for safety at 6 months (Eastwood et al., 2020) Intention-to-treat analysis (n=27)	
Parameter	**Result**
Device-related serious adverse events (primary endpoint)	None
Serious adverse events related to the surgical procedure	Local infection requiring explantation after 2 or 3 months and healing without consequences (n=3)
Other serious adverse events	Impaired swallowing leading to hospital stay prolonged by 1 day, resolving spontaneously (n=1)
Device-related non-serious adverse events	Local skin irritation due to the disposable patch (30%), persistent in one p. after 6 months; tongue abrasion (11%); tongue fasciculations (11%); discomfort due to electrical stimulation (11%)
Non-serious adverse events related to the surgical procedure	Impaired or painful swallowing (30%); dysarthria (26%); hematoma (19%); swelling or bruising around incision site (19%)

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Short-term results of upper airway stimulation in obstructive sleep apnea patients: the Amsterdam experience (Vonk et al., 2020) (89)	
Conclusion: Upper airway stimulation is an effective and safe treatment in obstructive sleep apnea patients with continuous positive airway pressure intolerance or failure. There was no significant difference in surgical outcome between patients with tongue base collapse with or without complete anteroposterior collapse at the level of the palate.	
General information about the study (Vonk et al., 2020)	
Study design / centers (country)	Single-center, retrospective, descriptive cohort study; Netherlands
Inclusion / exclusion criteria	AHI 15-65 events/h; central apnea index < 25% of AHI; non-supine AHI < 10 events/h; BMI < 32kg/m²; CPAP failure or intolerance; no complete concentric collapse at the level of the velum
Number of patients (p.)	47 p. identified; 44 p. evaluated; exclusion: 2 p. declined titration, 1 p. due to delayed healing
Patient (p.) characteristics	Age 58.5±9.6 years; 86.4% men (38/44); BMI 27.24±2.4kg/m²; complete anteroposterior collapse of the tongue base (n=44) with partial (n=9) or complete (n=33) collapse of the velum
Procedure / period	Baseline PSG; implantation of UAS (Inspire Medical Systems, Golden Valley, MN, USA); activation of stimulation approximately 1 month after implantation; titration of stimulation and outcome measurement (PSG) at 2 months; subgroup analysis for surgical success: 1st: p. with complete collapse of the tongue base with or without partial collapse of the palate, 2nd: p. with partial or complete collapse of the tongue base and complete collapse of the palate

Outcomes for efficacy at 2 months compared to baseline (Vonk et al., 2020) (n=44)	
Parameter	**Result**
Surgical success according to Sher criteria (responder) Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	88.6% of p. (n=39); reasons for non-responders: (temporary) increase in combined and central apneas (n=1), sufficient titration not possible due to frequent awakening caused by strength of the stimulation (n=3), neuropraxia of the hypoglossal nerve after postoperative bleed (n=1) No significant difference between subgroups with different collapse pattern (p=0.784)
Apnea-hypopnea index (AHI)	Median decrease from 37.6 (1st/3rd quartile: 30.4/43.4) to 8.3 (1st/3rd quartile: 5.3/12.0) events/h (p<0.001)
Obstructive apnea index	Median decrease from 11.8 (1st/3rd quartile: 2.7/18.9) to 0.8 (1st/3rd quartile: 0.0/2.2) events/h (p<0.001)
Supine AHI	Median decrease from 45.8 (1st/3rd quartile: 34.1/65.0) to 15.4 (1st/3rd quartile: 7.2/27.8) events/h (p<0.001)

Outcomes for efficacy at 2 months compared to baseline (Vonk et al., 2020) (n=44)	
Non-supine AHI	Median decrease from 26.2 (1st/3rd quartile: 17.5/35.9) to 5.2 (1st/3rd quartile: 2.4/10.0) events/h (p<0.001)
Percentage of total sleep time in supine position	Median decrease from 26.9% (1st/3rd quartile: 10.2%/51.2%) to 11.0% (1st/3rd quartile: 0.0%/41.3%) (p=0.021)
Minimum oxygen saturation	Median increase from 84.0% (1st/3rd quartile: 81.0%/87.0%) to 88.0% (1st/3rd quartile: 87.0%/90.0%) (p<0.001)
Oxygen desaturation index (ODI) (≥ 3% m)	Median decrease from 37.1 (1st/3rd quartile: 28.4/42.6) to 15.9 (1st/3rd quartile: 11.3/21.6) events/h (p<0.001)

Outcomes for safety at 2 months (Vonk et al., 2020) (n=44)	
Parameter	**Result**
Therapy-related adverse events	39 events in 26 p.: stimulation-related discomfort (incl. insomnia, arousal) (n=20; 45.5% of p.); tongue abrasion or dry mouth (n=8; 18.2% of p.); revision of sensor lead (n=5; 11.4% of p.); buzzing noise during stimulation (n=2; 4.5% of p.); temporary tongue weakness (n=2; 4.5% of p.); other 2 events (n=1 each; 2.3% of p.)

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Effect of Upper Airway Stimulation in Patients with Obstructive Sleep Apnea (EFFECT): A Randomized Controlled Crossover Trial (Heiser et al., 2021) (35) NCT03760328	
Conclusion: In comparison with sham stimulation, therapeutic UAS reduced OSA severity, sleepiness symptoms, and improved quality of life among participants with moderate-to-severe OSA.	
General information about the study (Heiser et al., 2021)	
Study design / centers (country)	Multicenter, randomized, double-blinded crossover trial with subtherapeutic sham stimulation (sham-controlled); 3 centers: Germany
Inclusion / exclusion criteria	Implantation of a stimulator for HGNS at least 6 months prior to study entry; moderate to severe OSA (AHI ≥ 15 events/h); CPAP intolerance; no complete concentric retropalatal collapse
Number of patients (p.)	89 p. included and randomized: 45 p. in the therapeutic stimulation (Stim) group, 44 p. in the sham stimulation (sham) group; 86 p. evaluated; exits: 2 p. in the Stim group at week 1 (no reason given); 1 p. in the Sham group at week 2 (due to stroke)
Patient (p.) characteristics	All patients (n=89): Age 57.5±9.8 years; 81% men; BMI 29.2±4.4 kg/m²; 100% "Caucasian"; ESS 7.0±4.4 points (ESS before implantation 10.6±3.8 points); AHI 8.3±8.9 events/h (AHI before implantation 32.3±11.4 events/h); no significant differences between Stim and Sham groups; no significant difference in the mean treatment duration before study entry (Stim group: 33.9±22.6 months, Sham group: 26.4±15.4 months (p=0.07))
Procedure / period	Baseline PSG with therapeutic stimulation; 1:1 randomization into 2 groups: Stim (therapeutic stimulation with an amplitude of 1.6 V±0.7 V on average) and Sham (placebo stimulation with lower amplitude of 0.1 V without therapeutic effect); first outcome measurement (PSG) after 1 week; switch from therapeutic to sham stimulation in the Stim group and from sham to therapeutic stimulation in the Sham group; second outcome measurement (PSG) after 2 weeks

Outcomes for efficacy after one week (Heiser et al., 2021) Fulfillment of the two co-primary endpoints is a prerequisite for further examination in the cross-over study design 2 exits in the Stim group rated as non-responders (intention-to-treat analysis (ITT)) (n=86)	
Parameter	**Result**
Responder rate (AHI ≤ 15 events/h) (co-primary endpoint)	Significant difference between treatment and sham: 73.7% of p. (33/45) vs. 29.5% of p. (13/44); difference: 43.8% of p. (CI: 25.1;62.5; p<0.001)
Apnea-hypopnea index (AHI) ≤ 10 events/h (percentage)	Significant difference between treatment and sham: 51.1% of p. (23/45) vs. 15.9% of p. (7/44)
Apnea-hypopnea index (AHI) ≤ 5 events/h (percentage)	Significant difference between treatment and sham: 35.6% of p. (16/45) vs. 0.0% of p. (0/44)
Daytime sleepiness (by ESS) (co-primary endpoint)	Significant difference between treatment and sham: 0.4±2.3 vs. 5.0±4.6 points; difference: 4.6 (CI: 3.1;6.1) points (p=0.001); large effect size (1.07 according to Cohen's d method); superiority of treatment (difference > 2 points)

Outcomes for efficacy: change from baseline after treatment or sham stimulation (1 week each) (Heiser et al., 2021) (n=86)	
Parameter	**Result**
Daytime sleepiness (by ESS)	Significant difference between treatment and sham: -3.3 (CI: -4.4; -2.2) points (p<0.001); sham stimulation: average increase by 3.5 (CI: 2.6;4.4) points
Quality of life (by FOSQ)	Significant difference between treatment and sham: 2.1 (CI: 1.4; 2.8) points (p<0.001); sham stimulation: average decrease by 1.9 (CI: 2.6;1.2) points
Apnea-hypopnea index (AHI)	Significant difference between treatment and sham: -15.5 (CI: -18.3; -12.8) events/h (p<0.001); sham stimulation: average increase by 16.1 (CI: 13.7;18.4) events/h
Oxygen desaturation index (ODI)	Significant difference between treatment and sham: -12.2 (CI: -14.8; -9.6) events/h (p<0.001); sham stimulation: average increase by 12.7 (CI: 10.3; 15.2) events/h
Apnea index	Significant difference between treatment and sham: -8.4 (CI: -10.6; -6.2) events/h (p<0.001); sham stimulation: average increase by 8.9 (CI: 7.2; 10.7) events/h
Supine AHI	Significant difference between treatment and sham: -21.6 (CI: -27.2; -16.0) events/h (p<0.001); sham stimulation: average increase by 23.8 (CI: 19.4; 28.2) events/h

Continued: Outcomes for efficacy: change from baseline after treatment or sham stimulation (1 week each) (Heiser et al., 2021) (n=86)	
Non-supine AHI	Significant difference between treatment and sham: -3.3 (CI: -6.4; -0.1) events/h (p=0.044); sham stimulation: average increase by 3.1 (CI: 0.1; 6.1) events/h
AHI in REM sleep	Significant difference between treatment and sham: -15.1 (CI: -19.7; -10.5) events/h (p<0.001); sham stimulation: average increase by 17.1 (CI: 13.5; 20.6) events/h
AHI in non-REM sleep	Significant difference between treatment and sham: -15.7 (CI: -18.5; -12.8) events/h (p<0.001); sham stimulation: average increase by 15.7 (CI: 13.3;18.2) events/h
Central apnea index	No significant difference between treatment and sham; difference: -0.1 (CI: -0.4; 0.1) events/h (p=0.285)
Mixed apnea index	No significant difference between treatment and sham; difference: -0.2 (CI: -0.6;0.2) events/h (p=0.355)
Central mixed apnea index	No significant difference between treatment and sham; difference: -0.4 (CI: -1.2;0.4) events/h (p=283)
Hypopnea index	Significant difference between treatment and sham: -7.0 (CI: -8.9; -5.1) events/h (p<0.001); sham stimulation: average increase by 7.0 (CI: 5.4;8.6) events/h
Minimal measured oxygen saturation	Significant difference between treatment and sham: -3.1% (CI: 2.1;4.2; p<0.001); sham stimulation: average decrease by 4.0% (CI: -5.0; -3.0)
Mean oxygen saturation	No significant difference between treatment and sham; difference: 0.3% (CI: -0.5;1.1; p=0.493)
Total time with oxygen saturation < 90%	Significant difference between treatment and sham: -6.6 (CI: -11.2; -2.0; p=0.005); sham stimulation: average increase by 9.0 (CI: 4.9;13.0)
Syndromic improvement rated by the physician investigators (by the Clinical Global Impression of Improvement scale (CGI-I))	Treatment: improvement in 76% of p. (n=86); sham: worsening in 95% of p. (n=87)

Outcomes for safety (Heiser et al., 2021) (n=89)	
Parameter	**Result**
Serious adverse events	Stroke in 1 p. in the sham group during stimulation treatment, unrelated to treatment, complete recovery
Non-serious adverse events	None

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2. Stimulation Therapy for Apnea Reduction (STAR) trial

Upper-Airway Stimulation for Obstructive Sleep Apnea (Strollo et al., 2014) (84) (first publication of the STAR trial (1/7) NCT01161420)	
Conclusion: In this uncontrolled cohort study, upper airway stimulation led to significant improvements in objective and subjective measurements of the severity of obstructive sleep apnea.	
General information about the study (Strollo et al., 2014)	
Study design / centers (country)	International, multicenter, prospective, single-arm, nonrandomized trial; 22 centers: United States, France, Germany, Netherlands, Belgium; followed by a randomized controlled trial (RCT)
Inclusion / exclusion criteria	Difficulty accepting or adhering to CPAP therapy; exclusion: AHI < 20 or > 50 events/h; percentage of central or mixed sleep-disordered breathing events > 25% of all apneas and hypopneas; non-supine AHI < 10 events/h; BMI > 32.0 kg/m^2; complete concentric collapse at the retropalatal airway; inclusion criterion for RCT: response to therapy (responders) after 12 months
Number of patients (p.)	126 p. implanted and at 2- to 9-month follow-up; 124 p. at 12-month follow-up; exits: 1 p. died due to myocardial infarction, 1 p. explant at patient's request; RCT: 46 p. randomized and evaluated
Patient (p.) characteristics	Mean of 2 examinations (before and 1 month after implantation) constitutes baseline values: age 54.5±10.2 years; 83% men (105/126 p.); BMI 28.4±2.6 kg/m²; systolic blood pressure 128.7±16.1 mmHg; diastolic blood pressure 81.5±9.7 mmHg; neck size 41.2±3.2 cm; 97% "white race"; 38% of p. (48 p.) with hypertension; 17% of p. (22 p.) with previous uvulopalatopharyngoplasty
Procedure / period	First baseline PSG; implantation of the "upper-airway stimulation system" (Inspire Medical Systems); second baseline PSG and activation of stimulation 1 month after implantation; titration of stimulation after 2 and 6 months; outcome measurement after 2 (PSG/ESS), 3, 6 (PSG/ESS), 9, and 12 (PSG/ESS) months; subsequent RCT: consecutive 1:1 randomization into 2 groups: Maintenance (ON) or withdrawal (OFF) of stimulation; outcome measurement (PSG) after 1 week (for details of the RCT part, see "Randomized Controlled Withdrawal Study of Upper Airway Stimulation on OSA", (Woodson et al., 2014) (75))

Outcomes for efficacy at 12 months compared to baseline (Strollo et al., 2014) Single-arm study (n=124, 2 exits counted as non-responders)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease by 68% (-16.4±16.7; median -17.3) from 32.0±11.8 (median 29.3) to 15.3±16.1 (median 9.0) events/h (p<0.001)
Oxygen desaturation index (ODI) (primary endpoint)	Average decrease by 70% (-14.6±15.8; median -15.7) from 28.9±12.0 (median 25.4) to 13.9±15.7 (median 7.4) events/h (p<0.001)
AHI responder rate (≥ 50% reduction from baseline and < 20 events/h at 12 months). (co-primary endpoint)	66% of p. (83/126 p.), exceeding the primary efficacy objective of 50% of p.
ODI responder rate (≥ 25% reduction from baseline) (co-primary endpoint)	75% of p. (94/126 p.), exceeding the primary efficacy objective of 50% of p.
Quality of life (by FOSQ)	Average increase by 2.9±3.1 (median 2.4) from 14.3±3.2 (median 14.6) to 17.3±2.9 (median 18.2) points (p<0.001)
Daytime sleepiness (by ESS)	Average decrease by 4.7±5.0 (median -4.0) from 11.6±5.0 (median 11.0) to 7.0±4.2 (median 6.0) points (p<0.001)
Sleep duration with oxygen saturation < 90% (percentage of sleep time)	Average decrease by 2.5%±11.1% (median -2.2%)) from 8.7%±10.2% (median 5.4%) to 5.9%±12.4% (median 0.9%) (p=0.01)
Duration of use (patient reported)	Daily use: 86% of p. (106/123 p.); use ≥ 5 days/week: 93% of p. (115/123 p.); stimulation time: 2.6 h/night on average

RCT part: Outcomes for efficacy in the groups with and without stimulation at 1 week compared to baseline (12-month value of the single-arm study) (Strollo et al., 2014) (n=23 each) (For details, see "Randomized Controlled Withdrawal Study of Upper Airway Stimulation on OSA" (Woodson et al., 2014) (75))	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Group without stimulation: average increase by 18.2 from 7.6 to 25.8 events/h (p<0.001); group with stimulation: no significant change; mean difference of change: 16.4±12.0 events/h (p<0.001)
Oxygen desaturation index (ODI)	Group without stimulation: average increase by 17.0 from 6.0 to 23.0 events/h; group with stimulation: no significant change

Outcomes for safety at 12 months (Strollo et al., 2014) Single-arm study (n=126)	
Parameter	**Result**
Device-related serious adverse events	Repositioning and fixation of neurostimulator due to discomfort (n=2)
Serious adverse events unrelated to the surgical procedure or the implant	n=33
Total serious adverse event rate	< 2% of p.
Device-related non-serious adverse events	Discomfort from electrical stimulation: 40% of p.; tongue soreness including abrasion: 21% of p.; AE temporary or resolved by adjustment of stimulation variables or by a tooth guard (n=9)
Non-serious adverse events related to the surgical procedure	Occurred within 30 days after implantation: 88% of AE (expected postsurgical AE, e.g., sore throat from intubation, pain at the incision site, muscle soreness); temporary tongue weakness: 18% of p. (no permanent tongue weakness reported)

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Randomized Controlled Withdrawal Study of Upper Airway Stimulation on OSA: Short- and Long-term Effect (Woodson et al., 2014) (75) (second publication of the STAR trial (2/7) NCT01161420)	
Conclusion: Withdrawal of therapeutic upper airway stimulation results in worsening of both objective and subjective measures of sleep and breathing, which when resumed results in sustained effect at 18 months. Reduction of obstructive sleep apnea severity and improvement of quality of life were attributed directly to the effects of the electrical stimulation of the hypoglossal nerve.	
General information about the study (Woodson et al., 2014)	
Study design / centers (country)	Multicenter, prospective, randomized controlled trial (RCT); for details of the baseline STAR trial see "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84)
Inclusion / exclusion criteria	Successful treatment at 12 months in the STAR trial (responders): at least 50% reduction in AHI compared to baseline and AHI < 20 events/h; for criteria of the baseline STAR trial see "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84)
Number of patients (p.)	46 p. included and randomized; 23 p. in the group with stimulation ("ON"), 23 p. in the group without stimulation ("OFF"); exits: 1 p. in the ON group after the RCT phase "lost to follow-up"
Patient (p.) characteristics	Demographic characteristics comparable to the baseline STAR trial population (see "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84)); no significant difference between randomized groups
Procedure / period	After 12 months of treatment with the "upper-airway stimulation system" (Inspire Medical Systems) in the baseline STAR trial, 1:1 randomization into 2 groups: Maintenance ("ON") or withdrawal ("OFF") of stimulation; outcome measurement (PSG) after 1 week; then continuation of therapy for all p.; outcome measurement (PSG) after 18 months; for baseline STAR trial see "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84)

Outcomes for efficacy **Comparison of groups with and without stimulation** (n=23 each) related to baseline values and outcomes at 12 months, after randomized phase with treatment withdrawal (RCT, 1 week) and after 18 months (n=22 with stimulation) (Woodson et al., 2014)	
Parameter	**Result**
Apnea Hypopnea Index (AHI) (primary endpoint)	Baseline: No significant difference between groups (31.3±12.3 vs. 30.1±11.4 events/h (difference: p=0.73)) 12 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (7.2±5.0 vs. 7.6±4.0 events/h (difference: p=0.74)) RCT: Significant difference between groups (16.9 (CI: -24.7; -9.0) events/h (p<0.001)); with stimulation: unchanged significant improvement vs. baseline (8.9±9.1 events/h (p<0.05)); without stimulation: no significant difference from baseline (25.8±16.2 events/h) 18 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (9.6±11.3 vs. 10.7±7.3 events/h (difference: p=0.85))
Oxygen desaturation index (ODI) (primary endpoint)	Baseline: No significant difference between groups (26.7±13.0 vs. 26.8±10.2 events/h (difference: p=0.98)) 12 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (6.3±5.4 vs. 6.0±3.7 events/h (difference: p=0.81)) RCT: Significant difference between groups (15.1 (CI: -22.7; -7.5) events/h (difference: p<0.001)); with stimulation: unchanged significant improvement vs. baseline (8.0±8.9 events/h (p<0.05)); without stimulation: no significant difference from baseline (23.0±15.6 events/h) 18 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (8.6±11.0 vs. 9.1±6.1 events/h (difference: p=0.86))

Continued: Outcomes for efficacy **Comparison of groups with and without stimulation** (n=23 each) related to baseline values and outcomes at 12 months, after randomized phase with treatment withdrawal (RCT, 1 week) and after 18 months (n=22 with stimulation) (Woodson et al., 2014)	
Oxygen saturation < 90% (percentage of sleep time)	Baseline: No significant difference between groups (7.4%±8.3% vs. 5.6%±4.4% (difference: p=0.35)) 12 months: Improvement in both groups vs. baseline (significant in the group without stimulation (p<0.05)); no significant difference between groups (3.2%±8.3% vs. 1.0%±2.0% (difference: p=0.23)) RCT: No significant difference between groups (-3.3% (CI: -8.4%;1.9%) (difference: p=0.20)); with stimulation: significant improvement vs. baseline (4.2%±6.2% (p<0.05)); without stimulation: no significant difference from baseline (7.5%±10.5%) 18 months: No significant difference between groups (7.6%±17.8% vs. 1.7%±6.2% (difference: p=0.12)); with stimulation: no significant difference from baseline (7.6±17.8%); without stimulation: significant improvement vs. baseline (1.7%±6.2% (p<0.05))
Sleep fragmentation (by arousal index)	Baseline: No significant difference between groups (30.9±13.5 vs. 26.2±14.6 events/h (difference: p=0.26)) 12 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (12.0±5.0 vs. 13.9±8.0 events/h (difference: p=0.35)) RCT: Significant difference between groups (17.7 (CI: -25.8; -9.6) events/h (difference: p<0.001)); with stimulation: unchanged significant improvement vs. baseline (13.2±9.9 events/h (p<0.05)); without stimulation: no significant difference from baseline (30.9±16.4 events/h) 18 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (14.8±10.4 vs. 17.2±9.9 events/h (difference: p=0.43))

Continued: Outcomes for efficacy **Comparison of groups with and without stimulation** (n=23 each) related to baseline values and outcomes at 12 months, after randomized phase with treatment withdrawal (RCT, 1 week) and after 18 months (n=22 with stimulation) (Woodson et al., 2014)	
Quality of life (by FOSQ)	Baseline: No significant difference between groups (15.1±3.1 vs. 13.9±2.6 points (difference: p=0.15)) 12 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (17.9±2.9 vs. 17.0±3.5 points (difference: p=0.36)) RCT: Significant difference between groups (2.9 (CI: 0.8;5.0) points) (difference: p=0.008)); with stimulation: unchanged significant improvement vs. baseline (17.9±2.9 points (p<0.05)); without stimulation: no significant difference from baseline (15.0±4.0 points) 18 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (18.0±2.9 vs. 17.1±2.9 points (difference: p=0.29))
Daytime sleepiness (by ESS)	Baseline: No significant difference between groups (11.2±5.3 vs. 11.3±5.0 points (difference: p=0.97)) 12 months: Significant improvement in both groups vs. baseline (p<0.05), no significant difference between groups (5.9±3.4 vs. 6.9±4.6 points (difference: p=0.43)) RCT: Significant difference between groups (4.5 (CI: -7.5; -1.4) points (p=0.005)); with stimulation: unchanged significant improvement vs. baseline (5.6±3.9 points (p<0.05)); without stimulation: no significant difference from baseline (10.0±6.0 points) 18 months: Significant improvement in both groups vs. baseline (p<0.05); no significant difference between groups (6.0±3.7 vs. 8.0±4.4 points (difference: p=0.09))

Continued: Outcomes for efficacy **Comparison of groups with and without stimulation** (n=23 each) related to baseline values and outcomes at 12 months, after randomized phase with treatment withdrawal (RCT, 1 week) and after 18 months (n=22 with stimulation) (Woodson et al., 2014)	
Systolic blood pressure	No significant difference between groups at any time point; significant improvement in the stimulation group from 129.1±16.1 mmHg (baseline) to 122.8±12.6 mmHg at 12 months ($p<0.05$) and to 123.3±12.9 mmHg at 18 months ($p<0.05$)
Diastolic blood pressure	No significant difference between groups at any time point; significant improvement in the stimulation group from 80.3±9.8 mmHg (baseline) to 74.7±10.8 mmHg after RCT phase ($p<0.05$)
Snoring (percentage reported by patient and bed partner with no or soft snoring)	Improvement in both groups after 12 months; group without stimulation: significant decrease after RCT phase and return to 12-month level after 18 months

Outcomes for efficacy **Comparison of groups with** (n=23) **and without** (n=23) **stimulation** related to changes after RCT phase (1 week) and after 18 months (n=22 with stimulation) vs. 12 months (Woodson et al., 2014)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	RCT vs. 12 months: Significant difference between groups (16.4 (CI: 9.2;23.7) events/h ($p<0.001$)); change with stimulation: 1.7±6.4 events/h; change without stimulation: 18.2±15.6 events/h 18 months vs. 12 months: No significant difference between groups (0.2 (CI: -5.1;5.4) events/h ($p=0.69$)); change with stimulation: -2.0±10.1 events/h; change without stimulation: -3.1±8.0 events/h
Oxygen desaturation index (ODI) (primary endpoint)	RCT vs. 12 months: Significant difference between groups (15.4 (CI: 8.7;22.1) events/h ($p<0.001$)); change with stimulation: 1.6±5.8 events/h; change without stimulation: 17.0±14.5 events/h 18 months vs. 12 months: No significant difference between groups (0.36 (CI: -4.1;4.8) events/h ($p=0.62$)); change with stimulation: -1.9±9.0 events/h; change without stimulation: -3.1±6.5 events/h

Continued: Outcomes for efficacy **Comparison of groups with** (n=23) **and without** (n=23) **stimulation** related to changes after RCT phase (1 week) and after 18 months (n=22 with stimulation) vs. 12 months (Woodson et al., 2014)	
Oxygen saturation < 90% (percentage of sleep time)	RCT vs. 12 months: Significant difference between groups (5.4% (CI: 0.1%;10.7%) (p=0.04)); change with stimulation: -1.0% ±6.4%); change without stimulation: -6.5% ±10.8%. 18 months vs. 12 months: No significant difference between groups (-4.0% (CI: -11.4%;3.3%) (p=0.26)); Change with stimulation: -4.6% ±16.4%.; Change without stimulation: -0.7% ±2.0%
Sleep fragmentation (by Arousal index)	RCT vs. 12 months: Significant difference between groups (16.3 (CI: 8.0;24.6) events/h (p<0.001)); change with stimulation: 1.2±9.3 events/h) change without stimulation: 17.0±16.9 events/h 18 months vs. 12 months: No significant difference between groups (0.4 (CI: -5.4;6.2) events/h (p=0.97)); change with stimulation: -3.4±9.6 events/h; change without stimulation: -3.3±10.6 events/h
Sleep architecture (e.g. sleep stages (N1, N2, N3, REM), sleep efficiency)	No significant change
Quality of life (by FOSQ)	RCT vs. 12 months: Significant difference between groups (2.3 (CI: -3.8; -0.9) points (p=0.001)); change with stimulation: 0.0±1.0 points; change without stimulation: 2.3±3.0 points; 18 months vs. 12 months: No significant difference between groups (-0.1 (CI: -1.3;1.1) points (p=0.91)); change with stimulation: -0.1±1.6 points; change without stimulation: 0.0±2.3 points
Daytime sleepiness (by ESS)	RCT vs. 12 months: Significant difference between groups (4.2 (CI: 2.0;6.4) points (p<0.001)); change with stimulation: 0.3±1.8 points); change without stimulation: -3.8±4.6 points; 18 months vs. 12 months: No significant difference between groups (1.2 (CI: -1.0;3.5) points (p=0.26)); change with stimulation: -0.1±2.4 points; change without stimulation: -1.3±4.6 points

Continued: Outcomes for efficacy **Comparison of groups with** (n=23) **and without** (n=23) **stimulation** Related to changes after RCT phase (1 week) and after 18 months (n=22 with stimulation) vs. 12 months (Woodson et al., 2014)	
Systolic blood pressure	RCT vs. 12 months: No significant difference between groups (-1.4 (CI: -11.3; 8.5) mmHg (p=0.77)); change with stimulation: 0.8±12.0 mmHg; change without stimulation: 2.2±19.1 mmHg 18 months vs. 12 months: No significant difference between groups (0.8(CI: -7.9;9.6) mmHg (p=0.85)); change with stimulation: -0.4±9.8 mmHg; change without stimulation: -1.3±18.2 mmHg;
Diastolic blood pressure	RCT vs. 12 months: No significant difference between groups (3.3 (CI: -2.5;9.2) (p=0.26)); change with stimulation: 3.4±9.6 mmHg; change without stimulation: 0.0±9.4 mmHg 18 months vs. 12 months: No significant difference between groups (1.1 (CI: -4.4;6.6) (p=0.69)); change with stimulation: 1.3±8.8 mmHg; change without stimulation: 0.3±9.7 mmHg

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Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months (Strollo et al., 2015) (44) (third publication of the STAR trial (3/7) NCT01161420)	
Conclusion: 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 Sleep Questionnaire) without an increase of the stimulation thresholds or tongue injury at 18 mo of follow-up.	
General information about the study (Strollo et al., 2015)	
Study design / centers (country)	International, multicenter, prospective, single-arm study; 22 centers: USA, France, Germany, Netherlands, Belgium; (see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Inclusion / exclusion criteria	Difficulty accepting or adhering to CPAP therapy; exclusion: AHI < 20 or > 50 events/h; non-supine AHI < 10 events/h; central or combined apnea index > 25% of AHI; BMI > 32 kg/m^2; complete concentric collapse at the level of the velopharynx

Continued: General information about the study (Strollo et al., 2015)	
Number of patients (p.)	126 p. implanted; 124 p. at 12-month follow-up; 123 p. at 18-month follow-up; exits: 2 p. died unrelated to therapy, 1 p. explantation at patient's request
Patient (p.) characteristics	Mean of 2 examinations (before and 1 month after implantation) constitutes baseline values: age 54.5±10.2 years; 83% men (105/126 p.); BMI 28.4±2.6 kg/m²; systolic blood pressure 128.7±16.1 mmHg; diastolic blood pressure 81.5±9.7 mmHg; neck size 41.2±3.2 cm; 97% "Caucasian"; 17% of p. (22 p.) with previous uvulopalatopharyngoplasty
Procedure / period	Activation of stimulation 1 month after implantation of the Inspire Upper Airway Stimulation System; outcome measurement (PSG) after 12 and 18 months, including determination of 3 predefined functional thresholds (sensation (minimal perception), bulk motion of the tongue, discomfort) (see also baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84)

Outcomes for efficacy at 18 months compared to baseline (Strollo et al., 2015) (n=123)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease by 67.4% from 32.0±11.8 (median 29.3) to 14.1±14.4 (median 9.7) events/h; AHI < 5 events/h: 29% of p., AHI < 10 events/h: 52% of p., AHI < 15 events/h: 69% of p.
Oxygen desaturation index (ODI) (primary endpoint)	Average decrease by 67.5%, from 28.9±12.0 (median 25.4) to 12.7±13.5 (median 8.6) events/h
Responder rate (≥ 50% reduction in AHI and AHI < 20 events/h) (intention-to-treat analysis)	64% of p.
Quality of life (by FOSQ)	Average increase from 14.3±3.2 (median 14.6) to 17.3±3.0 (median 18.4) points; non-responders: 63% of p. with clinically relevant improvement of ≥ 2 points
Daytime sleepiness (by ESS)	Average decrease from 11.6±5.0 (median 11.0) to 7.0±4.0 (median 6.0) points; non-responders: 78% of p. with clinically relevant improvement of ≥ 2 points
Oxygen saturation < 90% (percentage of sleep time)	Average decrease from 8.7%±10.2% (median 5.4%) to 5.6%±11.9% (median 1.2%)

Outcomes for efficacy at 18 months compared to 12-month values (Strollo et al., 2015) (n=123)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	No significant change (p=0.33)
Oxygen desaturation index (ODI) (primary endpoint)	No significant change (p=0.32)
Quality of life (by FOSQ)	No significant change (p=0.97)
Daytime sleepiness (by ESS)	No significant change (p=0.61)
Oxygen saturation < 90% (percentage of sleep time)	No significant change (p=0.91)

Outcomes for thresholds of awake stimulation at 12 months (n=124) **compared to 1 month** (n=126) **and at 18 months** (n=123) **compared to 12 months (**n=124) (Strollo et al., 2015)	
Parameter	**Result**
Sensation (minimal stimulation level perceived by the p.)	12 months vs. 1 month: no significant change (p=1.00) 18 vs. 12 months: decrease from 1.13V±0.62V to 1.07V±0.55V (p=0.02)
Bulk motion of the tongue	12 months vs. 1 month: no significant change (p=0.51) 18 vs. 12 months: no significant change (p=0.38)
Discomfort (highest stimulation level tolerated by the p.)	12 months vs. 1 month: increase from 2.47V±0.85V to 2.85V±1.02V (p=<0.001) 18 vs. 12 months: decrease from 2.85V±1.02V to 2.69V±0.96V (p=0.02)

Outcomes for safety at a mean of 911.3±137.8 days (Strollo et al., 2015) (n=126)	
Parameter	**Result**
Device-related serious adverse events	Discomfort due to pulse generator: 1 p. due to downward migration, resolved by repositioning and fixation; 1 p. due to non-standard implantation site (lateral infraclavicular), resolved by repositioning
Device-related non-serious adverse events	Discomfort due to stimulation: 12% of p.; tongue soreness including tongue abrasion: 3% of p.; AE mostly temporary or resolved by adjustment of stimulation parameters
Non-serious adverse events related to the surgical procedure	Expected events after surgical intervention: 86% of events within the first 30 days after implantation

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Upper Airway Stimulation for Obstructive Sleep Apnea: Self-Reported Outcomes at 24 Months (Soose et al., 2016**)** (83) (fourth publication of the STAR trial (4/7) NCT01161420)	
Conclusion: In a selected group of patients with moderate to severe OSA and a body mass index ≤ 32kg/m², 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.	
General information about the study (Soose et al., 2016)	
Study design / centers (country)	International, multicenter, prospective, single-arm cohort study; 22 centers: USA, France, Germany, Netherlands, Belgium (see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Inclusion / exclusion criteria	Difficulty accepting or adhering to CPAP therapy; exclusion: AHI < 20 or > 50 events/h; percentage of central or combined sleep-disordered breathing > 25% of all apneas and hypopneas; non-supine AHI < 10 events/h.; BMI > 32.0 kg/m²; complete concentric collapse of the retropalatal airway (see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Number of patients (p.)	126 p. implanted; 124 p. at 12-month follow-up; 111 p. (88% of 126 p.) evaluated at 24 months; exits: 1 p. died due to cardiac cause, 1 p. elective explantation due to lack of satisfaction with therapy, 10 p. missed the 24-month follow-up, 3 p. "lost to long-term follow-up"
Patient (p.) characteristics	Mean of 2 examinations (before and 1 month after implantation) constitutes baseline values: age 54.5±10.2 years; 83% men (105/126 p.); BMI 28.4±2.6 kg/m²; 97% "Caucasian" (for details, see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Procedure / period	Follow-up every 6 months after implantation of the Inspire Upper Airway Stimulation System; outcome measurement (questionnaire) at 12 and 24 months (see also baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))

Outcomes for efficacy at 24 months compared to baseline (Soose et al., 2016) (n=111)	
Parameter	**Result**
Daytime sleepiness (by ESS)	Average decrease by 4.4 (CI: 3.4;5.4) points from 11.6 (standard error 0.4) to 7.1 (standard error 0.4) points ($p<0.01$) (large effect size (>0.8)); no significant change from 12-month score (7.0 (standard error 0.4) points); scores within normal range (< 10 points): Increase from 32.5% of p. to 74.8% of p. (after 12 months) and 77.5% of p. (after 24 months); relevant improvement (decrease > 2 points): 72% of p. (after 12 months) and 70% of p. (after 24 months); worsening (increase ≥ 2 points): 7% of p. (after 12 months) and 9% of p. (after 24 months)
Quality of life by FOSQ including 5 subscales)	Average increase by 3.0 (CI: 3.5;2.4;) from 14.3 (standard error 0.3) to 17.2 (standard error 0.3) points ($p<0.01$) (large effect size (>0.8)); no significant change from 12-month value (17.3 (standard error 0.3) points); significant improvement in all five FOSQ subscales with large (>0.8) effect size (activity, vigilance) or moderate (>0.5) effect size (productivity, social, intimacy), no significant changes from 12-month scores; scores within normal range (>17.9 points): Increase from 15.9% of p. to 54.5% of p. (at 12 months) and 53.2% of p. (at 24 months); clinically significant improvement (increase ≥2 points): 53% of p. (at 12 months) and 59% of p. (at 24 months); worsening (decrease ≥2 points): 3.3% of p. (at 12 months) and 5.4% of p. (at 24 months)
Quality of life (by FOSQ-10)	Average increase from 13.8 points (baseline) to 17.0 points (after 12 months) and 17.3 points (after 24 months)
Snoring intensity (reported by patient or bed partner)	No or soft snoring: Increase from 22% of p. to 88% of p. (after 12 months) and 91% of p. (after 24 months); partner leaves room due to snoring: average decrease from 30% to 3% of partners (after 12 and 24 months)

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Three-Year Outcomes of Cranial Nerve Stimulation for Obstructive Sleep Apnea: The STAR Trial (Woodson et al., 2016) (85) (fifth publication of the STAR trial (5/7) NCT01161420)	
Conclusion: Long-term 3-year improvements in objective respiratory and subjective quality-of-life outcome measures are maintained. Adverse events are uncommon. UAS is a successful and appropriate long-term treatment for individuals with moderate to severe OSA.	
General information about the study (Woodson et al., 2016)	
Study design / centers (country)	International, multicenter, prospective, single-arm cohort study; 22 centers: USA, France, Germany, Netherlands, Belgium (see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Inclusion / exclusion criteria	Difficulty accepting or adhering to CPAP therapy; exclusion: AHI < 20 or > 50 events/h; central or combined apnea index > 25% of AHI; non-supine AHI < 10 events/h; BMI > 32.0 kg/m^2; complete concentric collapse at the level of the velopharynx
Number of patients (p.)	126 p. implanted; 124 p. at 12-month follow-up; 123 at 24-month follow-up; 116 p. (92% of 126 p.) evaluated at 36 months, including 98 p. with voluntary PSG; exits: 3; explants: 2 p. at patient's request due to other sleep disorders, 1 p. due to septic arthritis; 3 p. died unrelated to therapy: 1 p. due to myocardial infarction, 1 p. due to cardiac arrest after a fall, 1 p. due to homicide; 4 p. "lost to follow-up" (see also baseline STAR rial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Patient (p.) characteristics	Evaluated p. (n = 116): age 54.3±10.3 years; BMI 28.6±2.6 kg/m² (for details, see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84)) No significant differences between baseline and follow-up groups; no significant differences in AHI and BMI of the 98 p. with voluntary PSG compared to baseline and 12-month values
Procedure / period	Activation of stimulation 1 month after implantation of the Inspire system (Inspire Medical Systems, Maple Grove, Minnesota); titration of stimulation after 2 to 6 months; follow-up every 6 months for 3 years; outcome measurement (PSG) after 12 and 18 months; outcome measurement (voluntary PSG) after 36 months (see also baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))

Outcomes for efficacy at 36 months compared to baseline and 12-month values (Woodson et al., 2016) Based on voluntary PSG (n=98)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	Average decrease by 18.8 (CI: 16.1;21.6) from 30.4±10.4 (median 28.2) to 11.5±13.9 (median 6.2) events/h (p<0.001); no significant change from 12-month value (p=0.20); AHI < 5 events/h: 44% of p., AHI < 10 events/h: 69% of p.
Oxygen desaturation index (ODI) (primary endpoint)	Average decrease by 18.0 (CI: 15.5;20.4) from 27.1±10.8 (median 24.3) to 9.1±11.7 (median 4.8) events/h (p<0.001); average decrease by 2.86 (CI: 0.4;5.3) from 12.0±13.6 events/h at 12 months (p=0.02)
Responder rate (> 50% reduction in AHI and AHI < 20 events/h)	74% of p.; consistent outcomes at 12, 18, and 36 months: 52% of p. (51/98 p.); no response status at any period: 9% of p. (9/98 p.); responder rate in the group without voluntary PSG (n=17): 54% of p. (at 12 months); negative correlation with baseline AHI (odds ratio: 0.95 (CI:0.93;0.99) (p=0.01))
Oxygen saturation < 90% (percentage of sleep time)	No significant change from baseline (p=0.06); no significant change (p=0.46) from improved 12-month value (decrease by 2.9% (CI: 1.0%;4.8%) (p=0.01))
Daytime sleepiness (by ESS) (n=113)	Average decrease by 4.3 (CI: 3.3;5.4) from 11.4±5.1 (median 11) to 7.0±5.0 (median 6) points (p<0.001); no significant change from 12-month value (p=0.92); values within normal range (≤ 10 points): Increase from 33% to 77% of p.
Quality of life (by FOSQ) (n=113)	Average increase by 2.7 (CI: 3.4;1.9) from 14.6±3.0 (median 15.1) to 17.4±3.5 (median 18.8) points (p<0.001); no significant change from 12-month value (p=0.20); values within normal range (>17.9 points): Increase from 15% to 63% of p.
Duration of use (patient-reported) (n=113)	Daily use: 81% of p.; use min 4 nights/week: 10 p.; use < 4 nights/week: 11 p. (due to: stimulation-related discomfort (n=5), forgot to turn on device (n=2), other sleep disorder (n=2), lost remote control (n=1), return to CPAP (n=1))

Outcomes for safety at 36 months (Woodson et al., 2016)	
Parameter	**Result**
Serious adverse events	Elective explantation: 1p. for insomnia, 1p. for septic arthritis. 2 p. died unrelated to disease or device: 1 p. due to cardiac arrest, 1 p. due to homicide

Continued: Outcomes for safety at 36 months (Woodson et al., 2016)	
Non-serious adverse events	Numbness at the incisional sites ≥ 12 months (3 p.); discomfort due to electrical stimulation (80 p. in 1st year, 23 p. in 2nd year, 24 p. in 3rd year); tongue abrasions (28 p. in 1st year, 4 p. in 3rd year), 12 p. with recurrent tongue abrasions or discomfort related to tongue movement along the teeth successfully treated with plastic dental guards

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Upper Airway Stimulation for Obstructive Sleep Apnea: Patient-Reported Outcomes after 48 Months of Follow-up (Gillespie et al., 2017) (82) (sixth publication of the STAR trial (6/7) NCT01161420)	
Conclusion: Upper airway stimulation maintained a sustained benefit in patient-reported outcomes (ESS, FOSQ, snoring) at 48 months in select patients with moderate to severe obstructive sleep apnea.	
General information about the study (Gillespie et al., 2017)	
Study design / centers (country)	International, multicenter, prospective, single-arm cohort study; 22 centers: USA, France, Germany, Netherlands, Belgium (see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Inclusion / exclusion criteria	Difficulty accepting or adhering to CPAP therapy; exclusion: AHI < 20 or > 50 events/h; central or combined apnea index > 25% of AHI; non-supine AHI < 10 events/h; BMI > 32.0 kg/m^2; complete concentric collapse at the level of the velopharynx
Number of patients (p.)	126 p. implanted; 95 p. (75% of 126 p.) at 48-month follow-up, of whom 91 p. (73% of 126 p.) evaluated (4 p. had incomplete data); exits: 3 p. died unrelated to device or disease: 1 p. cardiac arrest, 1 p. sudden cardiac death, 1 p. homicide; 3 elective explants; 25 p. "lost to follow-up" (15 p. missed the 48-month follow-up, 5 p. exited the study, 5 p. from three study sites subsequently closed)
Patient (p.) characteristics	P. at 48-month follow-up: (n=95): age 55.1±10.5 years; men 79/95; BMI 28.6±2.7 kg/m^2 ; no significant differences between baseline and p. evaluated; no significant differences from p. without 48-month follow-up (n=25) (for details, see "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Procedure / period	Activation of stimulation 1 month after implantation of the Inspire system (Inspire Medical Systems, Maple Grove, Minnesota); titration of stimulation after 2 to 6 months; follow-up every 6 months for 48 months; outcome measurement (PSG) after 12 and 18 months; outcome measurement (voluntary PSG) after 36 months; outcome measurement (questionnaire) after 48 months (see also baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))

Outcomes for efficacy at 48 months compared to baseline (Gillespie et al., 2017) (n=91)	
Parameter	**Result**
Daytime sleepiness (by ESS) (n=89)	Average decrease from 11.4±5.1 to 7.3±4.9 (median 6) points (p=0.01)
Quality of life (by FOSQ) (n=89)	Average increase from 14.6±3.0 to 17.5±2.9 (median 18.6) points (p=0.01)
Snoring intensity (reported by patient (n=89) or bed partner (n=92))	No or soft snoring: Average increase from 22% to 91% of p. and increase from 17% to 85% of partners
Duration of use (patient reported)	Daily use: 81% of p. 75/93); unchanged since 24-month follow-up

Outcomes for safety at 48 months (Gillespie et al., 2017) (n=126)	
Parameter	**Result**
Device-related serious adverse events	A total of 5 AE in 5 of 126 p. (4.0%); elective explantation: 3 p. (1 p. therapy non-responder, 1 p. (responder) due to septic sternoclavicular joint adjacent to device, 1 p. (responder) due to prolonged insomnia); replacement of device components: 2 p. in the period 36 to 48 months after implantation (1 p. sensing lead due to insulation breach, 1 p. stimulation lead and pulse generator with repositioning of electrode to improve therapy response)
Device-related non-serious adverse events	Overall, number of AE continued to decrease after the 36-month follow-up; discomfort due to electrical stimulation n=136 (73 (57.9%) of p.), tongue abrasion n=47 (33 (26.0%) of p.), dry mouth n=17 (16 (12.7%) of p.), mechanical pain associated with presence of the device n=13 (12 (9.5%) of p.), temporary internal device usability or functionality complaint n=24 (20 (15.9%) of p.), temporary external device usability or functionality complaint n=39 (30 (23.8%) of p.), other acute symptoms n=38 (30 (23.1%) of p.), mild infection n=1 (1 (0.8%) of p.)
Non-serious adverse events related to the surgical procedure	Postoperative discomfort related to incisions n=51 (37 (29.4%) of P.), postoperative discomfort independent of incisions n=42 (34 (27.0%) of p.), temporary tongue weakness n=34 (23 (18.3%) of p.), intubation effects n=18 (15 (11.9%) of p.), headache n=8 (8 (6.3%) of p.), other postoperative symptoms n=22 (14 (11.1%) of p., mild infection n=1 (1 (0.8%) of p.)

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Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes (Woodson et al., 2018) (58) (seventh publication of the STAR trial (7/7) NCT01161420)	
Conclusion: Improvements in sleepiness, quality of life, and respiratory outcomes are observed with 5 years of UAS. Serious adverse events are uncommon. UAS is a nonanatomic surgical treatment with long-term benefit for individuals with moderate to severe OSA who have failed nasal continuous positive airway pressure.	
General information about the study (Woodson et al., 2018)	
Study design / centers (country)	International, multicenter, prospective, single-arm cohort study; 22 centers: USA, France, Germany, Netherlands, Belgium (see baseline STAR trial: "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014. (84))
Inclusion / exclusion criteria	Difficulty accepting or adhering to CPAP therapy; exclusion: AHI < 20 or > 50 events/h; central or combined apnea index > 25% of AHI; non-supine AHI < 10 events/h; BMI > 32.0 kg/m^2; complete concentric collapse at the level of the velopharynx
Number of patients (p.)	126 p. implanted; 97 p. (78% of 126 p.) at 5-year follow-up, including 71 p. with voluntary PSG; exits: 5 p. died unrelated to therapy, 3 p. explantation of stimulator or stimulation system; 21 p. "lost to follow-up"
Patient (p.) characteristics	P. at 60-month follow-up: (n=97): age 54.5±10.3 years; BMI 28.6±2.5 kg/m^2; differences from p. without 60-month follow-up (n=29): higher baseline AHI, higher baseline ODI, lower baseline quality of life (FOSQ); other characteristics and responses to therapy without significant difference between groups (for details, see baseline STAR trial "Upper-airway stimulation for obstructive sleep apnea" (Strollo et al., 2014) (84))
Procedure / period	Follow-up every 6 months after implantation of the Inspire system (Inspire Medical Systems, Inc, Maple Grove, Minnesota) for 5 years; outcome measurement (PSG) at 12 and 18 months; outcome measurement (voluntary PSG) at 3 and 5 years; sensitivity analyses, including "best case" and "worst case" scenarios, to account for missing data

Outcomes for efficacy at 60 months compared to baseline (Woodson et al., 2018) based on voluntary PSG (n=71) or with imputation of last observation carried forward (LOCF) at 12, 18, or 36 months (n=126), multiple imputation, or "best case" and "worst case" scenarios; baseline values (n=126)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint)	PSG: average decrease from 32.0±11.8 (median 29.3) to 12.4±16.3 (median 6.2) events/h; results not significantly different in sensitivity analyses; AHI < 15 events/h: 78% of p.; AHI < 5 events/h: 44% of p.

Continued: Outcomes for efficacy at 60 months compared to baseline (Woodson et al., 2018) Based on voluntary PSG (n=71) or with imputation of last observation carried forward (LOCF) after 12, 18, or 36 months (n=126), multiple imputation, or "best case" and "worst case" scenarios; baseline values (n=126)	
Oxygen desaturation index (ODI) (primary endpoint)	PSG: average decrease from 28.9±18.2 (median 25.4) to 9.9±14.5 (median 4.6) events/h
Responder rate (> 50% reduction in AHI and AHI < 20 events/h)	PSG: 75% of p. (n=71); per LOCF: 63% of p. (n=126); negative correlation with baseline ODI (odds ratio 0.94 (CI: 0.88;0.99) (p=0.02))
Oxygen saturation < 90% (percentage of sleep time)	Unchanged (8.0% ±10.1% vs. 7.4% ±13.3% at 60 months)
Daytime sleepiness (by ESS)	Average decrease from 11.6±5.0 (median 11) to 6.9±4.7 (median 6) points; results not significantly different in sensitivity analyses; scores within normal range (>10 points): Increase from 33% to 78% of p.
Quality of life (by FOSQ)	Average increase from 14.3±3.2 (median 14.6) to 18.0±2.2 (median 18.7) points; results not significantly different in sensitivity analyses; scores within normal range (>17.9 points): Increase from 15% to 67% of p.
Sleep architecture	Sleep fragmentation (by arousal index): average decrease from 27.8±117 to 7.8±9.7 events/h (p<0.0001); sleep stages: no changes
Snoring (reported by bed partner)	Intrusive snoring: average decrease from 54% to 2% of partners; Soft or no snoring: Increase from 17% to 90% of partners
Duration of use (patient reported)	Daily use: 80% of p.

Outcomes for safety at 60 months (Woodson et al., 2018) (n=126)	
Parameter	**Result**
Device-related serious adverse events	6% of p. (8/126 p.) with 9 AE: repositioning of the neurostimulator and the sensing lead in 2 procedures due to discomfort (1 p.), repositioning of the stimulation lead due to unfavorable tongue movement pattern and to improve therapy response (1 p.), replacement of neurostimulator and sensing lead due to insulation failure with the sensing lead (4 p.), replacement of stimulation lead due to inadvertently cut of stimulation lead (1 p.)
Device-related non-serious adverse events	Discomfort due to electrical stimulation: decrease from 81 AE in the first year (in most cases resolved by adjustment of stimulation parameters) to 5 AE in the 5th year, a total of 60.3% (76/126 p.) of p. affected; tongue abrasion: decrease from 28 AE in the first year to 2 AE in the 5th year, a total of 27.0% (34/126 p.) of p. affected; other AE in the 5th year: temporary device usability or functionality complaint (n=6), dry mouth (n=3), other 4 events (n=1 each)

3. German Post-Market Study (GPM Study)

Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study (Heiser et al., 2017b) (81) (first publication of the German Post-Market Study (1/6) NCT02293746)	
Conclusion: Selective upper airway stimulation is a safe and effective therapy for patients with obstructive sleep apnea and represents a powerful option for its surgical treatment.	
General information about the study (Heiser et al., 2017b)	
Study design/ centers (country)	Multicenter, prospective, single-arm study; 3 centers: Germany
Inclusion / exclusion criteria	AHI 15-65 events/h; non-adherence to CPAP; exclusion: BMI > 35kg/m²; central apnea index > 25% of AHI; complete concentric collapse at the velopharynx
Number of patients (p.)	60 p. implanted; 56 p. evaluated; exits: 4 p. due to change of therapy (uvulopalatopharyngoplasty) after 2-month titration
Patient (p.) characteristics	Age 56.8±9.1 (37-75) years; 96.7% men (58/60 p.); BMI 28.8±3.6 (21.4-36.6) kg/m²; 15 p. surgically pretreated; 14 p. pretreated with oral appliance therapy
Procedure / period	Baseline examination (2 home polygraphies (level III)); implantation of the Inspire system (Inspire Medical Systems, Minneapolis, Minnesota); activation of stimulation 4 weeks after implantation; titration of stimulation after 2 to 6 months; outcome measurement (2 home polygraphies (level III)) after 6 months.

Outcomes for efficacy at 6 months compared to baseline (Heiser et al., 2017b) (n=56)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by 61%±24% from 31.2±13.2 (median 28.6) to 12.0±9.8 (median 8.3) events/h (p<0.001); AHI ≤ 5 events/h: 25% of p., AHI ≤ 10 events/h: 59% of p., AHI ≤ 15 events/h: 70% of p.
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	68% of p.; evaluation incl. 4 exited p. (n=60): 63% of p.
Apnea index	Average decrease from 18.1±14.7 (median 14.2) to 7.6±7.8 (median 4.9) events/h (p<0.001)
Hypopnea index	Average decrease from 13.0±7.2 (median 12.4) to 4.4±4.1 (median 3.2) events/h (p<0.001)
Central and combined apnea index	No significant change (p=0.27)
Oxygen desaturation index (ODI)	Average decrease from 27.6±16.4 (median 27.0) to 13.5±10.7 (median 9.6) events/h (p<0.001)
Minimum oxygen saturation	Average increase from 71.4%±11.4% (median 73.8%) to 80.4%±7.6% (median 81%) (p<0.001)
Average oxygen saturation	No significant change (p=0.41)
Oxygen saturation < 90% (duration)	No significant change (p=0.07)
Oxygen saturation < 90% (percentage of sleep time)	No significant change (p=0.26)
Daytime sleepiness (by ESS)	Average decrease from 12.8±5.4 (median 13.5) to 7.0±4.5 (median 6.0) points (p<0.001)
Quality of life (by (FOSQ)	Average increase from 13.2±3.5 (median 13.3) to 16.9±2.9 (median 17.8) points (p<0.001)
Duration of use (objective device data)	42.9±11.9 (9-64) h/week on average

Outcomes for safety at 6 months (Heiser et al., 2017b)	
Parameter	**Result**
Device-related adverse events	Painful stimulation in the period after therapy activation (3 p.: resolved in 2 p. without intervention, 1 p. with mild pain continues to be monitored); speech difficulties after therapy activation (1 p., resolved by reprogramming)
Adverse events related to the surgical procedure	Bleeding during tunneling of the stimulation lead (2 p.); postoperative pain related to the incision (5 p.); acute tongue numbness (1 p.) and dysarthria (1 p.) resolved within 2 months

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Effects of upper-airway stimulation on sleep architecture in patients with obstructive sleep apnea (Hofauer et al., 2017) (77) (second publication of the German Post-Market Study (2/6) NCT02293746)	
Conclusion: In conclusion, significant changes in sleep architecture of patients with OSA and sufficient treatment with UAS could be observed. A reduction of the amount of time spent in N1-sleep could be caused by treatment with UAS and the rebound of REM sleep, observed for the first time in a study on UAS, is also a potential marker of the efficacy of UAS on sleep architecture.	
General information about the study (Hofauer et al., 2017)	
Study design / centers (country)	Single-center subinvestigation of the German Post-Market Study; Germany (see "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))
Inclusion / exclusion criteria	All consecutive p. of the GPM study implanted between 07/2014 and 06/2015; AHI 15-65 events/h; central apnea index < 25%); nonadherence to CPAP (p. not willing to proceed CPAP therapy after attempt to use it for several days); exclusion: BMI > 35kg/m²; complete concentric collapse of the soft palate
Number of patients (p.)	26 p. implanted and evaluated
Patient (p.) characteristics	Age 60.2±9.3 years; men 96% (25/26 p.); BMI 29.0±3.1 kg/m²
Procedure / period	Baseline examination; implantation of the Inspire II Upper Airway Stimulation System (Inspire Medical Systems, Maple Grove, MN, USA); activation of stimulation 1 month (± 5 days) after implantation; titration of stimulation and 1st outcome measurement (PSG) at 2 months; 2nd outcome measurement (PSG) at 3 months

Outcomes for efficacy at 2 months compared to baseline (Hofauer et al., 2017) (n=26)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by 72.2% from 33.9±12.3 to 9.1±9.9 events/h (p<0.001)
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	81.8% of p.
Oxygen desaturation index (ODI)	Average decrease by 61.5% from 33.5±14.5 to 12.9±11.5 events/h (p<0.001)

Continued: Outcomes for efficacy at 2 months compared to baseline (Hofauer et al., 2017) (n=26)	
Average oxygen saturation	Average increase from 92.7% ±2.2% to 94.1% ±1.8% (p=0.002)
Minimum oxygen saturation	Average increase from 75.5%±10.9% to 84.4%±5.9% (p<0.001)
Oxygen saturation < 90% (percentage of sleep time)	Average decrease from 13.8%±23.3% to 6.8% ±17.9% (p=0.048)
Daytime sleepiness (by ESS)	Average decrease from 12.3±5.6 to 7.9±4.6 points (p<0.001)
Time in bed (TIB)	No significant change (p=0.402))
Sleep period time (SPT)	No significant change (p=0.286))
Total sleep time (TST)	No significant change (p=0.248); percentage of time in sleep stages: no significant change (p=0.898); percentage of time in bed: no significant change (p=0.518))
Sleep stages (percentages)	• Non-REM sleep 1: non-significant average decrease from 23.2% ±14.2% to 16.4% ±16.9% (p=0.067) • Non-REM sleep 2: no significant change (baseline: 57.7%±12.9% (p=0.813) • Non-REM sleep 3: no significant change (baseline: 9.2%±8.7% (p=0.760) • REM sleep: average increase from 9.5% ±5.0% to 15.7% ±11.2% (p=0.010)
Change between sleep stages (number)	Average decrease from 52.7±35.4 to 31.2±15.7 events (p=0.006)
Sleep latency	No significant change (p=0.366)
Arousals (number)	Average decrease from 148.7±90.3 to 91.2±68.9 events (p=0.001) and 15.2±9.8
Arousal index	Average decrease from 24.3±15.1 to 15.2±9.8 events/h (p=0.002)
Respiratory effort related arousals (RERA) (number)	Average decrease from 55.2±43.6 to 12.5±31.6 events (p<0.001)
RERA index	Average decrease from 9.3±7.1 to 1.9±4.0 events/h (p<0.001).
Movement arousals (number)	No significant change (p=0.361)
Movement arousal index	No significant change (p=0.619)
Change to wake (number)	Average decrease from 11.1±6.0 to 5.5±5.2 events (p=0.002)
Arousals per sleep stage (number)	• Non-REM sleep 1: average decrease from 42.0±41.8 to 23.8±35.8 events (p=0.032) • Non-REM sleep 2: average decrease from 75.0±50.2 to 49.8±36.5 events (p=0.003) • Non-REM sleep 3: no significant change (p=0.679) • REM sleep: no significant change (p=0.881)

Outcomes for efficacy at 3 months compared to baseline and 2-month values (Hofauer et al., 2017) (n=26)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 33.9±12.3 to 9.7±13.1 events/h (p<0.001); no significant change from 2-month value (p=0.911)
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	81.8% of p., unchanged from 2-month value
Oxygen desaturation index (ODI)	Average decrease from 33.5±14.5 to 13.8±16.3 events/h (p<0.001); no significant change from the 2-month value (p=0.883)
Average oxygen saturation	Average increase from 92.7% ±2.2% to 93.8% ±2.1% (p=0.034); no significant change from 2-month value (p=0.215)
Minimum oxygen saturation	Average increase from 75.5% ±10.9% to 84.5% ±5.2% (p<0.001); no significant change from 2-month value (p=0.927)
Oxygen saturation < 90% (percentage of sleep time)	Average decrease from 13.8% ±23.3% to 7.2% ±18.4% (p=0.058); no significant change from 2-month value (p=0.809)
Daytime sleepiness (by ESS)	No significant change compared to the 2-month value
Time in bed (TIB)	No significant change from baseline (p=0.506) and 2-month value (p=0.411)
Sleep period time (SPT)	No significant change from baseline (p=0.445) and 2-month value (p=0.156)
Total sleep time (TST)	No significant change from baseline (p=0.516) and 2-month value (p=0.191); percentage of sleep period time: no significant change from baseline (p=0.696) and 2-month value (p=0.828); percentage of time in bed: no significant change from baseline (p=0.519) and 2-month value (p=0.547)
Sleep stages (percentages)	• Non-REM sleep 1: average decrease from 23.2% ±14.2% to 16.0% ±13.0% (p=0.007); no significant change from 2-month value (p=0.864) • Non-REM sleep 2: No significant change from baseline (p=0.306) and 2-month value (p=0.356) • Non-REM sleep 3: No significant change from baseline (p=0.965) and 2-month value (p=0.854) • REM sleep: no significant change from baseline (p=0.055) and 2-month value (p=0.597)
Change between sleep stages (number)	Average decrease from 52.7±35.4 to 28.5±15.0 events (p=0.007); no significant change from 2-month value (p=0.208)

Continued: Outcomes for efficacy at 3 months compared to baseline and 2-month values (Hofauer et al., 2017) (n=26)	
Sleep latency	No significant change from baseline (p=0.561) and 2-month value (p=0.472)
Arousals (number)	Average decrease from 148.7±90.3 to 82.2±42.5 events (p=0.001); no significant change from 2-month value (p=0.422)
Arousal index	Average decrease from 24.3±15.1 to 15.0±7.5 events/h (p=0.002); no significant change from 2-month value (p=0.596)
Respiratory effort related arousals (RERA) (number)	Average decrease from 55.2±43.6 to 7.8±9.4 events (p<0.001); no significant change from 2-month value (p=0.533)
RERA index	Average decrease from 1.9±4.0 to 1.4±1.7 events/h (p<0.001); no significant change from the 2-month value (p=0.623)
Movement arousal (number)	No significant change from baseline (p=0.304) and 2-month value (p=0.465)
Movement arousal index	No significant change from baseline (p=0.777) and 2-month value (p=0.922)
Change to wake (number)	Average decrease from 11.1±6.0 to 5.0±3.5 events (p<0.001) No significant change from 2-month value (p=0.718)
Arousals per sleep stage	• Non-REM sleep 1: average decrease from 42.0±41.8 to 19.6±19.4 events (p=0.004); no significant change from 2-month value (p=0.968) • Non-REM sleep 2: No significant change from baseline (p=0.620) and 2-month value (p=0.065) • Non-REM sleep 3: No significant change from baseline (p=0.986) and 2-month value (p=0.631) • REM sleep: No significant change from baseline (p=0.171) and 2-month value (p=0.286)

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Outcome After One Year of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Post-Market Study (Steffen et al., 2018) (79) (third publication of the German Post-Market Study (3/6) NCT02293746)	
Conclusion: This study supported that UAS as a safe and effective treatment option for patients with OSA in routine clinical practice.	
General information about the study (Steffen et al., 2018)	
Study design / centers (country)	Multicenter, prospective, single-arm study; 3 centers: Germany
Inclusion / exclusion criteria	AHI 15-65 events/h; nonadherence to CPAP; exclusion: BMI > 35kg/m²; central sleep apnea > 25% of AHI; complete concentric collapse at the soft palate
Number of patients (p.)	60 p. implanted; 56 p. evaluated; exits: 1 p. explantation at patient's request; 3 p. "lost to follow-up"
Patient (p.) characteristics	Age 56.8±9.1 (37-75) years; men (58/60 p.); BMI 28.8±3.6 (21.4-36.6) kg/m²; pre-treatment in 33% of p. (20/60 p.): 15 p. failed oral appliance therapy, 14 p. received reconstructive surgery
Procedure / period	Baseline examination (2 home polygraphs (level III)); implantation of the Inspire system (Inspire Medical Systems, Minneapolis, Minnesota, USA); activation of stimulation 4 weeks after implantation; titration of stimulation after 2 to 6 months; outcome measurement (2 home polygraphs (level III)) after 6 and 12 months

Outcomes for efficacy at 12 months compared to baseline (Steffen et al., 2018) (n=56)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 31.2±13.2 (median 28.6) to 13.8±14.8 (median 9.5) events/h (p<0.05)
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	73% of p.; evaluation including exited p. (n=60): 68% of p.
Apnea index	Average decrease from 18.1±14.7 (median 14.2) to 9.5±13.2 (median 5.3) events/h (p<0.05)
Hypopnea index	Average decrease from 13.1±7.2 (median 12.4) to 4.3±4.4 (median 2.5) events/h (p<0.05)
Central and combined apnea index	No significant change (1.2±2.3 vs. 2.2±7.9 events/h)
Oxygen desaturation index (ODI)	Average decrease from 27.6±16.4 (median 27.0) to 13.7±14.9 (median 9.8) events/h (p<0.05)
Minimum oxygen saturation	Average increase from 71.4% ±11.4% (median 73.8%) to 80.9% ±6.4% (median 81.8%) (p<0.05)

Continued: Outcomes for efficacy at 12 months compared to baseline (Steffen et al., 2018) (n=56)	
Parameter	**Result**
Average oxygen saturation	No significant change (92.8%±1.9% vs. 93.7%±2.0%)
Oxygen saturation < 90% (duration)	No significant change (45.3±60.5 min. vs. 30.9±61.6 min.)
Oxygen saturation < 90% (percentage of sleep time)	No significant change (10.7%±13.9% vs. 7.5%±15.5%)
Daytime sleepiness (by ESS)	Average decrease from 12.8±5.3 (median 13) to 6.5±4.5 (median 6.5) points (p<0.05)
Quality of life (by FOSQ)	Average Increase from 13.7±3.6 (median 13.7) to 17.5±3.0 (median 18.6) points (p<0.05)
Duration of use (objective device data)	39.1±14.9 h/week on average; use ≥ 20 h/week: 89% of p.

Outcomes for safety at 12 months (Steffen et al., 2018)	
Parameter	**Result**
Device-related serious adverse events	1 explantation at patient's request for cosmetic and other personal reasons

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Patient-reported outcome: results of the multicenter German post-market study (Hasselbacher et al., 2018) (95) (fourth publication of the German Post-Market Study (4/6) NCT02293746)	
Conclusion: The more the patients benefit from UAS according to their self-reported outcome, the higher is the therapy use.	
General information about the study (Hasselbacher et al., 2018)	
Study design / centers (country)	Multicenter, prospective, single-arm study; 3 centers: Germany
Inclusion / exclusion criteria	AHI 15-65 events/h; nonadherence to CPAP; exclusion: BMI > 35kg/m²; central apnea index > 25% of AHI; complete concentric collapse at the soft palate (see "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))
Number of patients (p.)	60 p. implanted; 56 p. evaluated: exits: 4 p. due to change of therapy (uvulopalatopharyngoplasty) after 2-month titration (see "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b). (81))
Patient (p.) characteristics	Age 56.8±9.1 (37-75) years; 96.7% men (58/60 p.); BMI 28.8±3.6 (21.4-36.6) kg/m²; 15 p. surgically pretreated; 14 p. pretreated with oral appliance therapy (see "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))
Procedure / period	Activation of stimulation 1 month after implantation of the Inspire II system (Inspire Medical Systems, Minneapolis, USA); titration of stimulation after 2 months; outcome measurement (2 home polygraphs) after 6 and 12 months (see also "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))

Outcomes for efficacy at 12 months compared to baseline (Hasselbacher et al., 2018) (n=56)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 31.2±13.2 to 13.8±14.8 events/h (p<0.001)
Daytime sleepiness (by ESS)	Average decrease from 12.8±5.3 to 6.5±4.5 points (p<0.001); Result after 6 months: Average decrease to 7±4.5 points (p<0.001); values in normal range (<10 points): 73% of p.

Continued: Outcomes for efficacy at 12 months compared to baseline (Hasselbacher et al., 2018) (n=56)	
Quality of life (by FOSQ)	Average increase from 13.7±3.6 to 17.5±3 points (p<0.001); outcome at 6 months: Average increase to 17.5±2.8 points (p<0.001); scores in the normal range (>17.9 points): increase from 13% to 59% of p.
Snoring intensity (reported by bed partner; baseline n=56; 6-month n=53; 12-month n=52)	Partner leaves room due to snoring: Decrease from 75% to 8% of p.; soft snoring: 33% of p.; no snoring: 37% of p.; significant decrease of snoring p. in the two most severely affected categories (p<0.001)
Duration of use	5.6±2.1 h/night on average

Outcomes for patient questionnaire at 6 and 12 months (Hasselbacher et al., 2018) (n=56)	
Parameter	**Result**
Comparing "Inspire" to CPAP	“Much better”: 77% of p. at 6 and 12 months
Recommend "Inspire" to a friend or family	“Agree”: 21% of p. at 12 months "strongly agree”: 75% of p. at 12 months
Choose "Inspire" again	“Strongly agree”: 70% of p. at 6 months, 82% of p. at 12 months
Satisfaction with "Inspire" therapy	Satisfied ("extremely satisfied" or "somewhat satisfied"): 96% of p., of which "extremely satisfied": 82% of p., at 12 months

Outcomes for correlation between objective and patient reported parameters at 6 and 12 months (Hasselbacher et al., 2018) (n=56)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Strong correlation to questionnaire results regarding "comparing 'Inspire' to CPAP" at 6 (p≤0.01) and 12 months (p<0.001); correlation to "choose ‘Inspire’ again" (p<0.001) and "recommend 'Inspire' to a friend or family" (p=0.001) at 6 months
Duration of use (at 6 and 12 months)	Correlation to questionnaire results regarding "comparing 'Inspire' to CPAP" (p=0.010/p=0.001), "choose 'Inspire' again" (p=0.000/p=0.019) and "recommend 'Inspire' to a friend or family" (p=0.001/p=0.043) at 6 and 12 months; Correlation to quality of life (p≤0.05) at 6 and 12 months; correlation to daytime sleepiness (p≤0.05) at 6 months; Correlation to AHI (p=0.031) at 12 months; correlation to snoring intensity (p<0.001) at 12 months

Continued: Outcomes for correlation between objective and patient-reported parameters at 6 and 12 months, respectively (Hasselbacher et al., 2018) (n=56)	
Daytime sleepiness (by ESS)	Correlation to questionnaire results regarding "comparing 'Inspire' to CPAP" (p=0.040), "recommend 'Inspire' to a friend or family" (p=0.021), "choose 'Inspire' again" (p=0.019) and "satisfaction with 'Inspire' therapy" (p=0,022) at 6 months and to "recommendation of 'Inspire' to a friend or family" (p=0.024), "choose 'Inspire' again" (p=0.019) and "satisfaction with 'Inspire' therapy" (p=0.020) at 12 months; Correlation to duration of use at 6 months (p=0.004); No correlation to AHI response at 6 and 12 months
Quality of life (by FOSQ)	Correlation to duration of use at 6 months (p=0.002); no correlation to AHI response at 6 and 12 months

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Patient experience with upper airway stimulation in the treatment of obstructive sleep apnea (Hofauer et al., 2019) (78) (fifth publication of the German Post-Market Study (5/6) NCT02293746)	
Conclusion: This investigation on the sUAS therapy revealed a high adherence to the therapy. The AHI or daytime sleepiness do not have obvious influence on adherence. Patients expressed a positive attitude towards sUAS. These patient reports upon stimulation experiences are of great help to consult candidates for sUAS in future.	
General information about the study (Hofauer et al., 2019)	
Study design / centers (country)	Multicenter subinvestigation of the German Post-Market study: 2 centers: Germany (see also "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))
Inclusion / exclusion criteria	All consecutive p. implanted between July 2014 and December 2016; AHI >15 and <65 events/h; central apnea index < 25%; CPAP noncompliance (unwillingness to continue therapy after using CPAP for several days or multiple therapy attempts with CPAP in the past); exclusion: BMI > 35 kg/m²; complete concentric collapse at the soft palate (see "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b). (81))
Number of patients (p.)	102 p. (center 1: n=57, center 2: n=45) implanted and at 2-month follow-up; 84 p. at 3-month follow-up; 83 p. at 6-month follow-up; 58 p. at 12-month follow-up; 11 p. at 24-month follow-up; 1 p. at 36-month follow-up
Patient (p.) characteristics	Age 56.7±11.3 years; BMI 29.4±4.3 kg/m² (see also "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))
Procedure / period	Activation of stimulation 1 month after implantation of the Inspire II system (Inspire II Upper Airway Stimulation System, Inspire Medical Systems, Maple Grove, MN, USA); titration of stimulation at 2 months; outcome measurement (PSG) at 3 months; outcome measurement (home polygraphy) at 6 and 12 months and subsequently every 12 months (see also "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))

Outcomes for efficacy at last follow-up compared to baseline (Hofauer et al., 2019) (Baseline and 2-month values n=102; 3-month values n=84; 6-month values n=83; 12-month values n=58; 48-month values n=11; 36-month values n=1)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 32.8±13.9 to 12.6±13.4 events/h (p<0.001)
Oxygen desaturation index (ODI)	Average decrease from 27.6±17.6 to 12.0±14.0 events/h (p<0.001)
Daytime sleepiness (by ESS)	Average decrease from 12.9±4.6 to 7.0±4.6 points
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	75% of p.

Outcomes for adherence at 12 months (Hofauer et al., 2019) Implantation occurred 10.1 months prior to outcome measurement on average (n=102)	
Parameter	**Result**
Duration of use (objective device data)	40±14.2 h/week, corresponding to 5.7±2.0 h/night on average Use < 4 h/night: 25.5% of p. Application ≥ 4 h/night: 74.5% of p. Application ≥ 6 h/night: 50% of p.
Duration of use (patient reported)	6.8±0.9 days/week and 5-7 h/night on average
Pause function	Use during the night: 59.4% of p.; lower duration of use when using the pause function than without (5.4±1.9 vs. 6.2±2.1 h/night (p = 0.041))
Change of the stimulation intensity	Never: 73.6% of p.; once a month: 17.0% of p.; once a week: 7.5% of p.; several times a week or daily: 2 p.

Outcomes for the subjective sensation and side effects of stimulation (Hofauer et al., 2019) (n=102)	
Parameter	**Result**
Sensing of the stimulation	During activation: 93 p.; during night: 50 p. (49.0%); sometimes awoken by therapy: 14 p. (13.7%); when awake due to other reasons: 80.2% of p.; upon waking in the morning: 67.9% of p.; finding stimulation disruptive: 22.6% of p.; forgetting to turn off stimulation in the morning: 11 p. (10.8%)
Turning off therapy during the night (mainly as a consequence to discomfort from the stimulation)	Once a week: 20 p. (19.6%); several times a week: 10 p. (9.8%); every night: 2 p. (2.0%); lower duration of use when therapy was turned off at night than never turned off (4.7±1.9 vs. 6.2±1.9 h/night (p = 0.001))
Impairment of the tongue (mostly movability)	Total at 12 p.; less than once a week: 8 p.; more than once a week: 3 p.; daily: 1 p.
Impaired movement of the neck	4 p. (3,9%)
Impaired movement of the chest	6 p. (5,9%)

Outcomes for patient attitude towards selective upper airway stimulation (Hofauer et al., 2019) (1=strongly agree, 5=strongly disagree) (n=102)	
Parameter	**Result**
Reduction of the problems caused by the OSA	Strong agreement (mean 1.44)
Health improvement	Consent (mean 1.52)
Improving the quality of life	Consent (mean 1.51)
Best treatment for OSA	Strong agreement (mean 1.27)
Use of stimulation therapy as expected	Strong agreement (mean 1.37)

Outcomes for correlations (Hofauer et al., 2019) (Spearman's rank correlation coefficient: 0.80-1.00 = very strong correlation (c.), 0.60-0.79 = strong c., 0.40-0.59 = moderate c., 0.20-0.39 = weak c., 0.00-0.19 = very weak c.)	
Parameter	**Result**
Duration of use (objective device data)	Positive correlation to subjective duration of use per week and per night (r=0.433, p=0.024 and r=0.485, p<0.001, respectively)
Time span between implantation and result measurement	Positive correlation to responder rate (r=0.388, p<0.001); negative correlation to stimulation experienced as disruptive (r= -0.200, p=0.045); negative correlation to impaired movement of the chest (r= -0.266, p=0.007)
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	Positive correlation to absolute and relative AHI reduction (r=0.228 and r=0.543); negative correlation to postoperative ODI (r= -0.521)
Patient age	Positive correlation to better therapy adherence (r=0.211, p=0.42)
P.'s attitude toward: Reducing the problems caused by OSA	Negative correlation to absolute and relative AHI reduction (r= -0.299, p=0.003 and r= -0.244, p=0.018); negative correlation to responder rate (r= -0.280, p=0.006)
P.'s attitude toward: Health Improvement, Improving the quality of life, best treatment for OSA, use of stimulation therapy as expected	Negative correlation to the duration of use (r= -0.299 to -0.238, p=0.022 to 0.027)
Outcomes for the subjective sensation and side effects of stimulation	No correlation to therapy adherence

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Long-term follow-up of the German post-market study for upper airway stimulation for obstructive sleep apnea (Steffen et al., 2020) (80) (sixth publication of the German Post-Market Study (6/6) NCT02293746)	
Conclusion: The German multi-center long-term outcomes compare favorably with previously published studies. Respiratory and sleepiness efficacy outcomes were sustained over 2 and 3 years, with a favorable safety profile, supporting the safety and efficacy of a chronic implantable therapy.	
General information about the study (Steffen et al., 2020)	
Study design/ centers (country)	Multicenter, prospective, single-arm study; 3 centers: Germany (see also "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))
Inclusion / exclusion criteria	AHI 15-65 events/h; CPAP intolerance; exclusion: BMI > 35kg/m²; central apnea index > 25% of AHI; complete concentric collapse at the velum
Number of patients (p.)	60 p. implanted, 41 p. at 24-month follow-up; 38 p. at 36-month follow-up; exits: 12 p. "lost to follow-up," 6 and 9 p., respectively, because of distance from clinic, 1 p. explantation of device; 1 p. died at third year unrelated to therapy
Patient (p.) characteristics	P. at 24-months follow-up (n=41): Age 57.4±9.7 (37-78) years; men/women 40/1 p.; BMI 28.9±3.5 kg/m² (22.5-36.6 kg/m²); no significant differences compared to p. without 24-month follow-up (n=19) except for AHI (p=0.03) and ODI (p=0.04) P. at 36-month follow-up (n=38): Age 58.0±10.0 (37-75) years; men/women 37/1 p.; BMI 29.1±3.9 kg/m² (22.5-36.6 kg/m²); no significant differences compared to p. without 36-month follow-up (n=22) except for duration of use (p<0.01) (see also "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))
Procedure / period	Baseline examination (2 home polygraphies); implantation of the Inspire system (Inspire Medical Systems, Minneapolis, MN, USA); activation of stimulation 4 weeks after implantation; titration of stimulation after 2 to 6 months; outcome measurement after 12 months; additional outcome measurement (home polygraphy) after 24 and 36 months (see also "Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study" (Heiser et al., 2017b) (81))

Outcomes for efficacy at 24 months compared to baseline (Steffen et al., 2020) (Baseline values n=60; 24-month values n=41)	
Parameter	**Result**
Daytime sleepiness (by ESS)	Average decrease score from 12.8±5.3 (median 13.0) to 5.3±4.6 (median 4.0) (p<0.05)
Apnea-hypopnea index (AHI)	Average decrease by 55% from 31.2±13.2 (median 28.6) to 10.9±8.3 (median 8.3) events/h (p<0.05)
Oxygen desaturation index (ODI)	Average decrease from 27.6±16.4 (median 27.0) to 11.4±11.5 (median 6.3) events/h (p<0.05)
Duration of use (objective device data)	40.3±14.7 (median 45.5) h/week on average; minimum 20 h/week: 92.5% of p.

Outcomes for efficacy at 36 months compared to baseline and 24-month values (Steffen et al., 2020) (Baseline values n=60; 36-month values n=38)	
Parameter	**Result**
Daytime sleepiness (by ESS)	Average decrease score from 12.8±5.3 (median 13.0) to 6.0±3.2 (median 6.0) (p<0.05)
Apnea-hypopnea index (AHI)	Average decrease by 58% from 31.2±13.2 (median 28.6) to 13.1±14.1 (median 10.0) events/h (p<0.05)
Oxygen desaturation index (ODI)	Average decrease from 27.6±16.4 (median 27.0) to 11.6±14.0 (median 8.3) events/h (p<0.05); no significant change from 24-month value (p=0.69)
Duration of use at 36 months	41.0±13.9 (median 44.5) h/week on average; minimum 20 h/week: 89.5% of p.

Outcomes for efficacy over time at 12, 24, and 36 months (Steffen et al., 2020) (Baseline values n=60; 24-month values n=41, 36-month values n=38)	
Parameter	**Result**
Daytime sleepiness (by ESS)	No significant change (p=0.51)
Apnea-hypopnea Index (AHI)	No significant change (p=0.54)
Oxygen desaturation index (ODI)	No significant change (p=0.69)
Duration of use	No significant change (p=0.69)

Outcomes for safety at 36 months (Steffen et al., 2020)	
Parameter	**Result**
Device-related serious adverse events	2 AE in 2 p. in the second and third year after implantation: replacement of the sensing lead (in 1 p. due to insulation damage) with return to therapy response

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4. Meta analyses

Hypoglossal Nerve Stimulation in the Treatment of Obstructive Sleep Apnea: A Systematic Review and Meta-analysis (Certal et al., 2015) (97)	
Conclusion: This review reveals that hypoglossal nerve stimulation therapy may be considered in selected patients with OSA who fail medical treatment. Further studies comparing hypoglossal nerve stimulation with conventional therapies are needed to definitively evaluate outcomes.	
General information about the study (Certal et al., 2015)	
Study design	Systematic literature search with qualitative and quantitative evaluation (meta-analysis per recommendations of the Cochrane Collaboration and the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement)
Inclusion / exclusion criteria	Primary study objective: efficacy of HGNS to treat OSA in adults; quantitative outcomes pre- and post-implantation of a HGNS neurostimulator, at minimum the following parameters: AHI, ODI, daytime sleepiness (ESS); exclusion: studies not including AHI, ODI, ESS, PSG data; pediatric populations
Number of studies and patients (p.)	6 studies evaluated: 5 prospective case series, 1 case report; total 200 p.; age 53.9±10.1 years
Procedure / period	Systematic literature search, last update: 09/05/2014; electronic database search: PubMed, Cochrane Library, Scopus; manual search of abstracts and proceedings of relevant congresses and scientific forums in 2010-2013; meta-analysis: data analysis with heterogeneity: random effects model, data analysis without heterogeneity: fixed effects model; implanted systems: Inspire II Upper Airway Stimulation device (Inspire Medical Systems, Inc., Maple Grove, MN), HGNS System (Apnex Medical, Inc., St. Paul, MN), Aura6000 System (ImThera Medical, Inc., San Diego, CA); study periods: 6 to 12 months

Outcomes for efficacy at 3 months compared to baseline (Certal et al., 2015) (n=34)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by 23.94 (CI: 31.45;16.43) or 54% from 43.90±17.61 to 20.03±14.15 events/h (p<0.001); no significant heterogeneity between studies
Oxygen desaturation index (ODI)	Average decrease by 10.04 (CI: 16.31;3.78) or 52% from 21.54±16.35 to 10.37±11.14 events/h (p<0.01); no significant heterogeneity between studies
Daytime sleepiness (by ESS)	Average decrease by 4.04 (CI: 6.45;1.90) from 11.60±5.26 to 7.44±4.53 points (p<0.001); no significant heterogeneity between studies

Outcomes for efficacy at 6 months compared to baseline (Certal et al., 2015) (n=60)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by 25.60 (CI: 31.18;20.01) or 57% from 43.73±16.55 to 18.91±16.47 events/h (p<0.001); no significant heterogeneity between studies
Oxygen desaturation index (ODI)	Average decrease by 11.68 (CI: 17.16;6.19) or 52% from 20.53±15.91 to 9.8±16.40 events/h (p<0.001); no significant heterogeneity between studies
Daytime sleepiness (by ESS)	Average decrease by 3.82 (CI: 5.37;2.27) from 11.95±4.68 to 8.14±3.97 points (p<0.001); no significant heterogeneity between studies

Outcomes for efficacy at 12 months compared to baseline (Certal et al., 2015) (n=170)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by 17.51 (CI: 20.69;14.34) or 50% from 35.45±13.26 to 17.55±16.94 events/h (p<0.001); no significant heterogeneity between studies
Oxygen desaturation index (ODI)	Average decrease by 13.73 (CI: 16.87;10.58) or 48% from 27.35±13.50 to 14.43±16.43 events/h (p<0.001); no significant heterogeneity between studies
Daytime sleepiness (by ESS)	Average decrease by 4.42 (CI: 5.39;3.44) from 11.63±5.01 to 7.23±4.13 points (p<0.001); no significant heterogeneity between studies

Outcomes for safety at 12 months (Certal et al., 2015) Qualitative evaluation (n=200)	
Parameter	**Result**
Serious adverse events	No AE resulting in life-threatening illness or injury or permanent impairment of body structure or function, no deaths
Device-related serious adverse events	Explantation: 9 p. (4.5% of p.)
Non-serious adverse events	Reported in all studies; usually temporary; no interference with activation of the device; e.g.: tongue weakness, tongue soreness, pain/swelling at the neck incision, fever, lack of tongue response to stimulation

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The outcomes of hypoglossal nerve stimulation in the management of OSA: A systematic review and meta-analysis (Kompelli et al., 2019) (96)	
Conclusion: HGNS is a safe and effective treatment for CPAP refractory OSA. Further study comparing HNS to other therapies is required.	
General information about the study (Kompelli et al., 2019)	
Study design / centers (country)	Systematic literature research with qualitative and quantitative evaluation (meta-analysis)
Inclusion / exclusion criteria	Primary study objective: role of HGNS in the treatment of sleep apnea in adults; exclusion: case reports, review articles, nonhuman studies, studies without AHI, ODI, daytime sleepiness (ESS) as primary endpoints
Number of studies and patients (p.)	16 studies identified in systematic literature search; 12 studies with a total of 381 p. evaluated in meta-analysis (cohort of STAR trial evaluated only once (largest cohort with the most complete follow-up data))
Procedure / period	Systematic literature search, start 08/14/2017; database search: PubMed, Cochrane Database, Scopus; meta-analysis: evaluation of results pre-procedure and 6 and 12 months post-procedure; data analysis with heterogeneity (heterogeneity test with p<0.05); random effects model, data analysis without heterogeneity: fixed effects model; high likelihood of publication bias in relation to the sample size of the studies

Outcomes for efficacy at 6 months compared to baseline (Kompelli et al., 2019)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (baseline n=286, 6-month n=266)	Average decrease by 23.47 (CI: 19.38;27.57) events/h (p<0.00001)
Oxygen desaturation index (ODI) (baseline n=256, 6-month n=250)	Average decrease by 13.38 (CI: 10.97;15.80) events/h (p<0.00001)
Daytime sleepiness (by ESS) (baseline n=248, 6-month n=242)	Average decrease by 4.95 (CI: 4.11;5.79) points (p<0.00001)
Quality of life (by FOSQ, SAQLI) (baseline n=217, 6-month n=213)	FOSQ: average increase by 3.12 (CI: 2.57;3.67) points (p<0.00001) SAQLI: average increase by 3.1 (CI: 2.6;3.8) points (p=0.008)

Outcomes for efficacy at 12 months compared to baseline (Kompelli et al., 2019)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (baseline n=271, 12-month n=265)	Average decrease by 21.08 (CI: 16.93;25.23) events/h (p<0.00001)
Oxygen desaturation index (ODI) baseline n=271, 12-month n=267)	Average decrease by 15.01 (CI: 12.68;17.35) events/h (p<0.00001); note: the confidence interval is given in the text as (CI: 13.3;16.7)
Daytime sleepiness (by ESS) (baseline n=261, 12-month n=252)	Average decrease by 5.03 (CI: 4.21;5.84) points (p<0.00001); note: in the text the following values are given: 4.8 (CI: 4.2;5.4) points
Quality of life (by FOSQ) (baseline n=217, 12-month n=211)	Average increase by 3.12 (CI: 2.57;3.67) points (p<0.00001)

Outcomes for safety (Kompelli et al., 2019)	
Parameter	**Result**
Adverse events	Pain: 6.2% (CI: 0.7%;16.6%) of p. (p<0.0001); tongue abrasion with or without lesions: 11.0% (CI: 1.2%;28.7%) of p. (p<0.0001); internal device malfunction: 3.0% (CI: 0.3%;8.4%) of p. (p=0.0001); external device malfunction: 5.8% (CI: 0.3%;17.4%) (p<0.0001); other AE: 7.0% (CI: 0.6%;19.2%) of p. (p<0.0001)

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Hypoglossal nerve stimulation long-term clinical outcomes: a systematic review and meta-analysis (Constantino et al., 2020) (98)	
Conclusion: HGNS has obtained a high surgical success rate with reasonable long-term complication rate related to the device implanted. The procedure represents an effective and safe surgical treatment for moderate-severe OSA in selected adult patients who had difficulty with accepting or adhering to CPAP treatment.	
General information about the study (Constantino et al., 2020)	
Study design / centers (country)	Systematic literature search with qualitative and quantitative evaluation (meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines)
Inclusion / exclusion criteria	Prospective studies assessing the efficacy of HGNS for OSA treatment in adults (according to PICOS); results at minimum on AHI, ODI, daytime sleepiness (ESS); comparison of baseline and post-implantation outcomes (without restriction of the study period); publication in an externally peer-reviewed journal; exclusion: redundant cohorts of the STAR trial and GPM study
Number of studies and patients (p.)	12 studies included in qualitative synthesis; 9 studies included in quantitative synthesis (meta-analysis); total of 350 p.; age (median) 54.3 (IQR 53;56.25) years; BMI (median) 29.8 (IQR 28.8-31.6) kg/m²
Procedure / period	Systematic literature search, last search: 11/17/2018; database search: PubMed/MEDLINE, Google Scholar, Cochrane Library; search of literature references in the identified publications; meta-analysis: data analysis with heterogeneity: random effects model, data analysis without heterogeneity: fixed effects model; subgroup analysis according to the implanted system ("Inspire" n=239 p., "Apnex" n=52 p., "ImThera" n=59 p.); subgroup analysis according to the study period (6 and 12 months)

Outcomes for efficacy at 6 months compared to baseline (Constantino et al., 2020) AHI: Random Effects Model, ODI and ESS: Fixed Effects Model	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by -18.35 (CI: -23.52; -13.19) events/h (p<0.001): Inspire: -17.74 (CI: -24.73; -10.14) events/h (p<0.001), weight: 61.9%; ImThera: -9.50 (CI: -19.14;0.14) events/h (p=0.05), weight: 12.7%; Apnex: -24.20 (CI: -30.94; -17.45) events/h (p<0.001), weight: 25.4%, significant heterogeneity across subgroups (p=0.05)
Oxygen desaturation index (ODI)	Average decrease by -12.95 (CI: -15.87; -10.03) events/h (p<0.001): Inspire: -14.65 (CI: -18.15; -11.16) events/h (p<0.001), weight: 69.8%; ImThera: -8.80 (CI: -18.23;0.63) events/h (p=0.07), weight: 9.6%; Apnex: -9.11 (CI: -15.53; -2.68) events/h (p=0.005), weight: 20.6%; no significant variability across subgroups (p=0.22)
Daytime sleepiness (by ESS)	Average decrease by -4.57 (CI: -5.47; -3.67) points (p<0.001): Inspire: -5.36 (CI: -6.64; -4.08) points (p<0.001), weight: 49.4%; ImThera: -3.70 (CI: -5.65; -1.75) points (p<0.001), weight: 21.3%; Apnex: -3.87 (CI: -5.53; -2.21) points (p<0.001), weight: 29.3%

Outcomes for efficacy at 12 months compared to baseline (Constantino et al., 2020) AHI, ODI, ESS: Fixed Effects Model	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease by -17.88 (CI: -20.27; -15.49) events/h (p<0.001): Inspire: -17.50 (CI: -20.01; -14.98) events/h (p<0.001), weight: 90.4%; ImThera: -24.20 (CI: -37.39;11.01) events/h. (p<0.001), weight: 3.3%; Apnex: -20.10 (CI: -29.62; -10.58) events/h (p<0.001), weight: 6.3%; no significant variability across subgroups (p=0.55)
Oxygen desaturation index (ODI)	Average decrease by -14.79 (CI: -17.26; -12.32) events/h (p<0.001): Inspire: -15.59 (CI: -18.21; -12.98) events/h, weight: 89.6%; ImThera: -13.90 (CI: -27.72; -0.08) events/h (p=0.05), weight: 3.2%; Apnex: -5.20 (CI: -14.40;4.00) events/h (p=0.27), weight: 7.2%; no significant variability across subgroups (p=0.10)
Daytime sleepiness (by ESS)	Average decrease by -5.01 (CI: -5.83; -4.18) points (p<0.001): Inspire: -5.27 (CI: -6.18; -4.35) points (p<0.001), weight: 80.6%; ImThera: -2.90 (CI: -6.97;1.17) points (p=0.16), weight: 4.1%; Apnex: -4.20 (CI: -6.30; -2.10) points (p<0.001), weight: 15.3%

Outcomes for efficacy at 6 and 12 months compared to baseline (Constantino et al., 2020) Qualitative evaluation	
Parameter	**Result**
Surgical success according to Sher criteria (responder) Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	At 6 months: Inspire: 70% of p. (n=115); ImThera: 35% of p. (n=46); Apnex: 59.8% of p. (n=115) At 12 months: Inspire: 72.4% of p. (n=211); ImThera: 76.9% of p. (n=13); Apnex: 55% of p. (n=31) At 18 months: Inspire: 64% of p. (n=123) At 36 months: Inspire: 74% of p. (n=113) At 60 months: Inspire: 75% of p. (n=71)
Duration of use (reported in 5 studies, n=139)	Median 5.8 (IQR 5.5;6.2) h/night; daily use: Inspire (patient-reported): 86% at 1 year, 81% at 3 years, 80% at 5 years

Outcomes for safety (Constantino et al., 2020) Qualitative evaluation	
Parameter	**Result**
Device-related serious adverse events (STAR trial)	At 5 years: 6% of p. (8/126) with surgical repositioning or replacement of neurostimulator or leads
Device-related non-serious adverse events (STAR trial)	Discomfort due to electrical stimulation: 60.3% of p. (n=76), 81 AE in the first and 5 AE in the 5th year after implantation; tongue abrasion: 27% of p. (n=34), 28 AE in the first and 2 AE in the 5th year after implantation;
Non-serious adverse events related to surgical intervention (STAR trial)	Discomfort related to incision: 30.2% of p. (n=52); discomfort independent of incision: 27% of p. (n=42); temporary tongue weakness: 18.3% of p. (n=23)
Serious adverse events (7 studies, n=195)	14 AE at 12 p. (6.1%); at least 1 AE related to surgical procedure: 81 p. (41.5%); at least 1 AE related to device: 56 p. (28.7%)

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5. ADHERE Registry

Upper Airway Stimulation for Obstructive Sleep Apnea: Results from the ADHERE Registry (Boon et al., 2018) (92) (first publication of the ADHERE Registry (1/4) NCT02907398)	
Conclusion: Across a multi-institutional registry, UAS therapy demonstrates significant improvement in subjective and objective OSA outcomes, good therapy adherence, and high patient satisfaction.	
General information about the study (Boon et al., 2018)	
Study design / centers (country)	Multicenter, retrospective and prospective study based on the ADHERE registry (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry: International, multicenter, non-interventional registry); 10 centers: USA, Germany
Inclusion / exclusion criteria	AHI 15-65 events/h; CPAP intolerance or inadequate adherence; favorable anatomic criteria established by previous studies
Number of patients (p.)	301 p. included (October 2016 to September 2017)
Patient (p.) characteristics	Age 59.2±11.2 years; 82% men (248/301 p.); BMI 29.2±3.8 kg/m²; "Caucasian" 97% (291/301 p.), "Black" 1% (4/301 p.), "Asian" <1% (1/301 p.), "American Indian or Alaska Native" <1% (1/301 p.), "Other" 1% (4/301 p.)
Procedure / period	Baseline PSG; implantation of the Inspire system (Inspire Medical Systems Inc., Maple Grove, Minnesota); activation of stimulation 1 month after implantation; titration of stimulation after 2 to 6 months; outcome measurement (PSG or home polygraphy) at a mean of 134 days (median 123 days)

Outcomes for efficacy at a mean of 134±76 (CI: 125.4;142.9) days compared to baseline (Boon et al., 2018)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (baseline n=293, outcome measure n=295)	Average decrease by 25.3±16.4 (71%±34%) from 35.6±15.3 (CI: 33.8;37.3) (median 32.5) to 10.2±12.9 (CI: 8.7;11.7) (median 5.5) events/h (p<0.0001); AHI ≤ 5 events/h: 48% of p.; AHI ≤ 10 events/h: 67% of p.; AHI ≤ 15 events/h: 81% of p.; no significant difference between retrospectively and prospectively collected data; AHI per PSG (9.1±12.4 events/h, n=212) lower than per home polygraphy (12.9±13.8 events/h, n=83) (p=0.02)
Reduction in mean AHI by ≥ 50% to < 20 events/h	78% of p.

Continued: Outcomes for efficacy at a mean of 134±76 (CI: 125.4;142.9) days compared to baseline (Boon et al., 2018)	
Daytime sleepiness (by ESS) (baseline n=261, outcome measure n=239)	Average decrease from 11.9±5.5 (CI: 11.2;12.6) (median 12) to 7.5±4.7 (CI: 6.9;8.1) (median 7) points, p<0.0001; percentage of p. with scores < 10 points: Increase from 38% to 67% of p.; no significant difference between retrospectively and prospectively collected data
Duration of use (objective device data)	6.5±2.3 h/night (CI: 6.1;6.9) on average (median 46 h/week); use > 20 h/week: 96% of p.
Assessment of the clinical improvement by the physician (by Clinical Global Impression of Improvement scale (CGI-I))	Improvement in 94% of p.
Therapy experience (patient report)	Preferring HGNS over CPAP: 90% of p.; choosing HGNS again: 96% of p.; recommending therapy to friends/family: 94% of p.; satisfied with therapy: 92% of p.

Outcomes for safety (Boon et al., 2018)	
Parameter	**Result**
Therapy-related adverse events	97% of procedures without AE; a total of 64 adverse events in 54 p. (18% of 301 p.), including: replacement of stimulation lead due to dislodged stimulation cuff: 1 p. one month postimplant; intraoperative bleeding during tunneling of the stimulation lead: 2 p.; seroma: 2 p.; submandibular swelling: 1 p.; tongue weakness: 1 p.; dysarthria: 1 p.

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Results of the ADHERE Upper Airway Stimulation Registry and Predictors of Therapy Efficacy (Thaler et al., 2020) (94) (second publication of the ADHERE Registry (2/4) NCT02907398)	
Conclusion: Across a multi-institutional study, UAS therapy continues to show significant improvement in subjective and objective OSA outcomes. This analysis shows that the therapy effect is durable and adherence is high.	
General information about the study (Thaler et al., 2020)	
Study design / centers (country)	Cohort study based on the ADHERE registry (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry: International, multicenter, non-interventional registry); 10 centers: USA, Germany
Inclusion / exclusion criteria	AHI 15-65 events/h; CPAP intolerance; no complete concentric collapse
Number of patients (p.)	640 p. evaluated at 6-month follow-up and 382 p. evaluated at 12-month follow-up; a total of 1,017 p. included in registry (October 2016 to February 2019)
Patient (p.) characteristics	Age 60±11 years; BMI 29.3±3.9 kg/m²; 74% men; "Caucasian" 96%; most common comorbidity: hypertension (48% of p.); pre-treatments: 97% of p. CPAP therapy, 20% of p. oral appliances, 22% of p. nasal procedures, 29% of p. palatal procedures, 5% of p. tongue-base procedures
Procedure / period	Baseline examination; implantation of the Inspire system (Inspire Medical Systems Inc., Maple Grove, MN); first outcome measurement (PSG or type 3 home polygraphy after titration) approximately 6 months after implantation; second outcome measurement (PSG or type 3 home polygraphy) approximately 12 months after implantation; post hoc logistic regression analysis of predictors of treatment success, univariate analysis, followed by multivariate analysis and sensitivity analysis to test the robustness of the predictors identified (odds ratio (OR) > 1: treatment success more likely; odds ratio (OR) < 1: treatment success less likely)

Outcomes for efficacy at 6 months compared to baseline (Thaler et al., 2020) (n=640)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 35.8±15.4 (median 32.8) to 11.0±13.5 (median 6.3) events/h (p<0.001)
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	83% of p. (485/582 p.)
Daytime sleepiness (by ESS)	Average decrease from 11.4±5.6 (median 11.0) to 7.7±4.8 (median 7.0) points (p<0.0001); scores within normal range (ESS < 10 points): Increase from 37% to 67% of p.

Outcomes for efficacy at 12 months compared to baseline (Thaler et al., 2020) (n=382)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (n=381)	Average decrease from 35.8±15.4 (median 32.8) to 14.2±15.0 (median 9.5) events/h (p<0.001)
Responder rate according to Sher criteria Measurement of treatment success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113)	69% of p. (265/381 p.)
Daytime sleepiness (by ESS)	Average decrease from 11.4±5.6 (median 11.0) to 7.2±4.8 (median 6.0) points (p<0.0001); values within normal range (ESS < 10 points): Increase from 37% to 74% of p.
Duration of use (objective device data)	5.6±2.1 (median 5.7) h/night on average
Assessment of the clinical improvement by the physician	Improvement in 92% of p.
Therapy experience (patient report)	Preferring HGNS over CPAP: 95% of p.; choosing HGNS again: 94% of p.; recommending therapy to friends/ family: 96% of p.; satisfied with therapy: 93% of p.

Outcomes for efficacy: predictors of therapy response according to Sher criteria (Thaler et al., 2020) (reduction in AHI by at least 50% and an absolute AHI below 20 events/h (113))	
Parameter	**Result**
Positive predictors (OR > 1)	Female sex: 90% increased probability of therapy response (univariate analysis: OR=1.943 (CI: 1.013;3.729) (p=0.0457), multivariate analysis: 3.413 (CI: 1.452;8.019) (p=0.0049))
Negative predictors (OR < 1)	Baseline BMI: 8.5% increased probability of therapy response per unit decrease (univariate analysis: OR=0.915 (CI: 0.863;0.970) (p=0.0028), multivariate analysis: 0.909 (CI: 0.851;0.972) (p=0.0050));

Outcomes for safety at 6 months (Thaler et al., 2020)	
Parameter	**Result**
Adverse events	161 AE in 71 p. (46% of p.): stimulation-related discomfort: 41 AE in 12% of p.; activation-related AE: 37 AE in 3% of p.; incision-related discomfort: 14 AE in 4% of p.; tongue abrasions 12 AE in 3% of p.; device-related discomfort: 10 AE in 3% of p.; insomnia/arousal: 10 AE in 3% of p.; and other AE
Adverse events requiring surgical intervention	Electrode dislodgement: 1 p.

Outcomes for safety at 12 months (Thaler et al., 2020)	
Parameter	**Result**
Adverse events	113 AE in 49 p. (32% of p.): Stimulation-related discomfort: 28 AE in 8% of p.; activation-related AE: 23 AE in 7% of p.; insomnia/arousal: 17 AE in 5% of p.; tongue abrasion: 14 AE in 4% of p.; incision-related discomfort: 8 AE in 2% of p.; device-related discomfort: 5 AE in 1% of p.; and other AE
Adverse events requiring surgical intervention	Electrode repositioning: 2 p.

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Upper Airway Stimulation versus Untreated Comparators in Positive Airway Pressure Treatment-Refractory Obstructive Sleep Apnea (Mehra et al., 2020) (76) (third publication of the ADHERE Registry (3/4) NCT02907398)	
Conclusion: Objective and subjective sleep apnea burden was more improved in those receiving upper airway stimulation versus not. Results underscore the need to optimize clinical care pathways focused on effective treatment of obstructive sleep apnea patients not upper airway stimulation–insurance eligible and prioritize public health policy initiatives to address insurance-based sex-specific disparities.	
General information about the study (Mehra et al., 2020)	
Study design / centers (country)	Prospective, comparative, parallel-arm study based on the ADHERE registry (ADHERE- (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry: International, multicenter, non-interventional registry); 9 centers: USA (6), Germany (3)
Inclusion / exclusion criteria	AHI 15-65 events/h; < 25% central and combined apneas; continuous PAP intolerance; no complete concentric collapse at the soft palate; presence of medical insurance and approval request prior to the surgical procedure; criteria for implantation according to Boon et al, 2018 (92))
Number of patients (p.)	350 p. included: therapy group: 250 p., comparison group: 100 p.; exclusion: 20 p. from therapy group due to missing data
Patient (p.) characteristics	Age and BMI comparable in both groups (therapy group: age 57.5±10.8 years, BMI 29.8±3.9 kg/m^2; comparison group: age 57.3±8.4 years, BMI 29.3±3.9 kg/m^2); higher percentage of women in the comparison group than in the therapy group (p<0.004) (therapy group: 84% men (194/230 p.); comparison group: 70% men (67/100 p.)); percentage of p. with previous sleep surgery greater in the therapy group than in the comparison group (therapy group: 52% (119/230 p.); comparison group: 27% (27/100 p.)
Procedure / period	Baseline PSG/home polygraphy; division of p. into 2 groups based on insurance coverage before treatment: coverage approval (therapy group) and coverage denial (comparison group); therapy group: implantation of Inspire system (Inspire Medical Systems) and titration of stimulation; comparison group: no or other therapy; outcome measure (type III home polygraphy): therapy group: planned after 6 months (actually 4-24 months), comparison group: within 24 months after insurance denial

Outcomes for efficacy after 360±171 (median 175) days (treatment group) and after 272±278 (median 358) days (comparison group): Comparison of the therapy group (n=230) **to the comparison group** (n=100) (Mehra et al., 2020)	
Parameter	**Result**
Apnea-hypopnea index (AHI) (primary endpoint) (therapy group: n=228)	Significantly greater decrease in the therapy group: (p<0.001): Therapy group: average decrease by 19.1±15.8 from 33.7±13.4 to 14.7±13.8 events/h; comparison group: average decrease by 8.1±20.9 from 34.9±16.4 to 26.8±17.6 events/h; no significant difference in baseline values (p=0.95)
Daytime sleepiness (by ESS) (primary endpoint)	Significant difference between groups (p<0.001) with improvement in therapy group and worsening in comparison group: therapy group: Average decrease by 5.1±5.5 from 12.3±5.5 to 7.2±4.8 points; comparison group: Average increase by 1.8±3.7 from 10.9±5.4 to 12.8±5.2 points; no significant difference in baseline scores (p=0.06)
Oxygen desaturation index (ODI) (therapy group: n=219, comparison group n=96)	Significantly lower value in the therapy group (p<0.001): Therapy group: 14.1±14.1 (median 9.2) events/h; comparison group: 25.5±17.9 (median 20.8) events/h
Oxygen saturation < 90% (percentage of time) (therapy group: n=135, comparison group: n=98)	No significant difference between groups (p=0.98): Therapy group: 17.7%±25.7% (median 4.0%), comparison group: 14.6%±22.9% (median 3.5%)
Arterial oxygen nadir (therapy group: n=220, comparison group: n=99)	Significantly lower value in the therapy group (p<0.02): therapy group: 81.6%, comparison group: 79.9%
Quality of life (by FOSQ-10) (therapy group: n=221, comparison group: n=75)	Significantly higher score in the therapy group (p<0.001): Therapy group: 17.1±3.2 (median 18.0) points; comparison group: 12.4±3.7 (median 12.0) points
Duration of use (objective device data)	5.6±2.0 h/night on average; use > 20 h per week: 92% of p.; use > 28 h per week: 77% of p.
Assessment of the clinical improvement by the physician (by Clinical Global Impression of Improvement scale (CGI-I))	Therapy group: (significant) improvement in 93% of p.; comparison group: (significant) improvement in 4% of p.
Therapy experience (patient report)	Choose therapy again: 95% of p.; (very) satisfied with therapy: 95% of p.
Therapy choice of the p.	Therapy group: HGNS mono-therapy: 96% of p., additional OSA surgery: 3% of p., return to PAP: 1% of p.; comparison group: no therapy: 86% of p., return to PAP: 7% of p., use of oral appliance: 3% of p., additional OSA surgery: 3% of p., PAP combined with oral appliance: 1% of p.

Outcomes for safety (Mehra et al., 2020)	
Parameter	**Result**
Serious adverse events	2 surgical revisions in 1 p. due to feeling of tension in the neck caused by adhesions, resolved by replacement of the stimulation lead and subplatysmal plane tunneling
Non-serious adverse events related to the surgical procedure	A total of 3% of p. affected: incision-related discomfort (1.4%, 3 p.); swallowing/speech effects (0.5%, 1 p.); device-related discomfort (0.5%, 1 p.); other AE (1.0%, 2 p.).
Therapy-related non-serious adverse events	A total of 10% of p. affected: Tongue abrasion (2.9%, 6 p.); stimulation-related AE (1.9%, 4 p.); other complaints (1.0%, 2 p.); other AE (4.3%, 9 p.)

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Hypoglossal Nerve Stimulation Usage by Therapy Non-responders (Coca et al., 2021) (93) (fourth publication of the ADHERE Registry (4/4) NCT02907398)	
Conclusion: Patients classified as NR to upper airway stimulation continue to use therapy with improvement in percent time of sleep with O_2 <90%, reduction in daytime sleepiness, and improvement in quality of life. Therefore, ongoing usage of the device should be encouraged in NR patients who note improvement while integrating additional strategies to lower the long-term effects of OSA.	
General information about the study(Coca et al., 2021)	
Study design / centers (country)	Retrospective database analysis (ADHERE- (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry) Registry: international, multicenter, noninterventional registry)
Inclusion / exclusion criteria	AHI 15-65 events/h; BMI ≤ 35 kg/m²; no complete concentric airway collapse; CPAP-intolerance
Number of patients (p.)	2,090 p. implanted; 966 p. at 12-month follow-up; 717 p. with data on responder status according to Sher criteria: Responder (R): 497 p. (69%); Non-Responder (NR): 220 p.; total of 2,168 p. included in registry (October 2016 to September 2020)
Patient (p.) characteristics	No significant differences between responders and non-responders except for BMI (p=0.004): responders: age 60.05±10.7 years; 78.59% men; BMI 28.91±3.8 kg/m²; non-responders: age 58.74±11.7 years; 80.91% men; BMI 29.84±4.0 kg/m²
Procedure / period	Baseline PSG/home polygraphy; implantation of the Inspire system (Inspire Medical Systems) and titration of stimulation; outcome measurement (PSG or home polygraphy) after 12 months with classification of p. according to Sher criteria into responders and non-responders (measurement of therapy success according to Sher: reduction of AHI by at least 50% and an absolute AHI below 20 events/h (113))

Non-responders: Outcomes for efficacy after titration compared to baseline (Coca et al., 2021) (n=220)	
Parameter	**Result**
Apnea-hypopnea index (AHI)	Average decrease from 33.0±10.0 to 14.45±9.45 events/h (p<0.001)
Oxygen desaturation index (ODI)	No significant change (p=0.225)
Oxygen saturation < 90% (percentage of sleep time)	No significant change (p=0.648)
Daytime sleepiness (by ESS)	Average decrease from 11.83±5.5 to 8.57±5.0 points (p<0.001)
Assessment of the clinical improvement by the physician (by Clinical Global Impression of Improvement scale (CGI-I))	(Very) strong improvement at 46.5% of p.
Apnea-hypopnea index (AHI)	Average decrease from 33.0±10.0 to 25.6±8.55 events/h (p<0.001)
Oxygen desaturation index (ODI)	No significant change (p=0.395)
Oxygen saturation < 90% percentage of sleep time).	No significant change (p=0.748)
Daytime sleepiness (by ESS)	Average decrease from 11.83±5.5 to 8.15±4.9 points (p<0.001)
Assessment of the clinical improvement by the physician (by Clinical Global Impression of Improvement scale (CGI-I))	No significant change compared to the value after titration (p=0.076)

Comparison of responders and non-responders after titration (Coca et al., 2021) (Number of patients (n) depending on the data completeness for the respective parameter)	
Parameter	**Result**
Therapy adherence	Significant difference (p=0.004): Responders: 91% of p. (n=429); Non-responders: 88% of p. (n=188)
Duration of use (objective device data)	Significant difference (p=0.016): Responders: 6.59±1.8 h/night on average (n=429); Non-responders: 6.28±1.97 h/night on average (n=188)
Oxygen desaturation index (ODI)	No significant difference between groups (p=0.343) (R: n=246, NR: n=110)
Oxygen saturation < 90% (percentage of sleep time)	No significant difference between groups (p=0.694) (R: n=64, NR: n=101)
Daytime sleepiness (by ESS)	No significant difference between groups (p=0.127) (R: n=404, NR: n=176)

Continued: Comparison of responders and non-responders after titration (Coca et al., 2021) (Number of patients (n) depending on the data completeness for the respective parameter)	
Assessment of the clinical improvement by the physician (by Clinical Global Impression of Improvement scale (CGI-I))	Significant difference (p<0.001): • (very) much improved (CGI-1 to 2): Responders: 88.4% (n=351); Non-responders: 46.5% (n=60) • minimally improved/no change/minimally worse (CGI-3 to 5): Responders: 11.6% (n=46); Non-responders: 51.9% (n=67) • (very) much worse (CGI-6 to 7): Responders: 0% (n=0); Non-responders: 1.6% (n=2)
Therapy adherence	Significant difference (p=0.005): Responders: 83% of p. (n=354); Non-responders: 72% of p. (n=130)
Duration of use (objective device data)	Significant difference (p=0.001): Responders: 5.89±2.0 h/night on average (n=428); Non-responders: 5.24±2.2 h/night on average (n=180)
Oxygen desaturation index (ODI)	Significant difference (p<0.001): Responders: 8.27±7.4 events/h (n=285); Non-responders: 25.72±15.7 events/h (n=123)
Oxygen saturation < 90% (percentage of sleep time)	No significant difference between groups (p=0.896) (R: n=229, NR: n=125)
Daytime sleepiness (by ESS)	Significant difference (p=0.001): Responders: 6.78±4.4 points (n=428); Non-responders: 8.15±5.0 points (n=185)
Assessment of the clinical improvement by the physician (by Clinical Global Impression of Improvement scale (CGI-I))	Significant difference (p<0.001): • (very) much improved (CGI-1 to 2): Responders: 85.6% (n=357) Non-responders: 56.9% (n=87) • minimally improved/no change/minimally worse (CGI-3 to 5): Responders: 13.4% (n=56) Non-responders: 41.8% (n=64) • (very) much worse (CGI-6 to 7): Responders: 1.0% (n=4) Non-responders: 1.3% (n=2)

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6. MAUDE database

Adverse events associated with the Inspire implantable hypoglossal nerve stimulator: A MAUDE database review (Bestourous et al., 2020) (99)	
Conclusion: In attempting to further improve patient compliance, understanding these device malfunctions and adverse events related to HNS implantation or usage is crucial for the identification of potential causes of patient non-adherence.	
General information about the study (Bestourous et al., 2020)	
Study design	Retrospective evaluation of the Manufacturer and User Facility Device Experience (MAUDE) database (FDA's publicly available database housing medical device reports)
Inclusion / exclusion criteria	Reports submitted between January 01, 2000, and May 31, 2020; exclusion: duplicates; patient-submitted reports; AE not attributable to the Inspire stimulator or its implantation; reports based on publications or information gathered on the Internet; or reports with insufficient information for analysis
Number of reports	204 reports identified; 180 reports of 196 adverse events evaluated
Procedure / period	Systematic search of the MAUDE database using product code "MNQ" for "Inspire stimulator for sleep apnea"; variables evaluated (including): event setting, adverse event to patient, iatrogenic injury, device malfunction, interventions, the root cause of the event cause (if reported), date of the event; event categories: intraoperative and postoperative

Reported events by category (Bestourous et al., 2020) (n=196)	
Parameter	**Result**
Intraoperative events	n=20 (10.2% of events)
AE to patient	n=1 (bradycardia and cardiac arrest with successful resuscitation)
Device malfunction	n=1 (faulty device placement)
Iatrogenic injuries	n=18 (pneumothorax/pleural rupture n=12, vascular injury n=4, musculoskeletal injury n=1, mucosal injury n=1)
Postoperative adverse events	n=176 (89.8% of the events)
AE to patient	n=145 (most common events: infection n=50, neuropraxia n=22, hematoma/seroma n=17, pain n=13, device migration n=12; device expulsion through the skin n=9; muscle tethering/lead traction n=6; overstimulation n=5; other 5 events: 3 events n=3, 2 events n=1)
Device malfunction	n=28 (sensing lead n=10, faulty device placement n=9, device control n=3, pulse generator n=2, stimulation lead n=2, unknown n=2)
Iatrogenic injuries	n=3 (vascular injury n=2, pneumothorax/pleural rupture n=1)

Reoperations by type and cause (Bestourous et al., 2020) (n=83 (42.3% of all events) in 75 patients)	
Parameter	**Result**
Reoperation due to AE to patient	n=65 (78.3% of all reoperations, 44.5% of all AE to patient); causes: infection n=21, device migration n=11, pain n=7, hematoma/seroma n=7, device expulsion through the skin n=7, muscle tethering/lead traction n=4, neuropraxia n=3, other 4 causes: 1 cause n=2, 3 causes n=1
Reoperation due to device malfunction	n=18 (21.7% of all reoperations, 62.1% of all device malfunctions); causes: faulty device placement n=8, sensing lead malfunction n=6, pulse generator malfunction n=2, stimulation lead malfunction n=2
Reoperation due to iatrogenic injuries	None

AE to patient by type of treatment/intervention (Bestourous et al., 2020) (n=146)	
Parameter	**Result**
Observation	n=30 (20.5% of events): neuropraxia n=13, pain n=5, hematoma/seroma n=5, muscle tethering/lead traction n=2, other 5 events n=1
Imaging	n=3 (2.1% of events): device migration n=2, infection n=1
Medical management	n=56 (38.4% of events); infection n=36, hematoma/seroma n=9, device expulsion through the skin n=5, allergic reaction n=2, neuropraxia n=2, other 2 events n=1
Evacuation	n=9 (6.2% of events): hematoma/seroma n=9
Debridement/incision and drainage	n=8 (5.5% of events): infection n=4, hematoma/seroma n=2, device expulsion through the skin n=2
Surgical revision	n=24 (16.4% of events): device dislocation n=9, pain n=5, muscle tethering/lead traction n=4, device expulsion through the skin n=4, other 2 events n=1
Device replacement	n=5 (3.4% of events): device migration n=3, infection n=1, overstimulation n=1
Explantation	n=31 (21.2% of events): Infection n=19, device expulsion through the skin n=3, hematoma/seroma n=2, neuropraxia n=2, other 5 events n=1
Discontinuation of therapy	n=12 (8.2% of events): neuropraxia n=5, overstimulation n=4, pain n=2, neck swelling n=1
Setting modulation	n=3 (2.1% of events): device migration n=2, tongue swelling n=1
Biopsy	n=2 (1.4% of events): hematoma/seroma n=1, sialorrhea n=1

♦ ♦ ♦ ♦

Adverse Events in Hypoglossal Nerve Stimulator Implantation: 5-Year Analysis of the FDA MAUDE Database (Bellamkonda et al., 2021) (60)	
Conclusion: Previous data have demonstrated hypoglossal nerve stimulator implantation results in reliable OSA improvement. However, a number of technical difficulties and complications still exist during the postoperative period, which should be communicated to patients during the surgical consent process.	
General information about the study (Bellamkonda et al., 2021) (60)	
Study design	Retrospective review of the Manufacturer and User Facility Device Experience (MAUDE) database (FDA's publicly available database housing medical device reports)
Inclusion / exclusion criteria	Reports submitted between May 2014 and September 2019
Number of reports	132 reports on 134 adverse events evaluated
Procedure / period	Systematic search in the MAUDE database using the terms: "Inspire" and "hypoglossal nerve stimulator"; evaluation of intra- and postoperative complications, need for revision surgery and need for device explant, differentiated by device component

Adverse events by device part and category (Bellamkonda et al., 2021)	
Parameter	**Result**
Adverse events related to the pulse generator	
Intra- and postoperative complications	73 p. (model 3024: 28 p.; model 3028: 45 p.); complications: infection 20 p.; pain 8 p., device migration 7 p., lisp 6 p., hematoma/seroma 6 p., facial nerve (VII) palsy 5 p., hypoglossal nerve (XII) palsy 5 p.; other 13 complications in 16 p. (1 complication 3 p., 1 complication 2 p. 11 complications 1 p. each)
Revision surgery	n=12 (model 3024: n=7; model 3028: n=5); complications: device migration n=7, Twiddler's syndrome n=2, pain n=1, dizziness/sweating/visual changes n=1, electrical leakage n=1)
Device explant	n=12 (model 3024: n=4; model 3028: n=8); complications: infection n=8, vocal cord weakness n=1, facial nerve (VII) palsy n=1, hematoma n=1, Twiddler's syndrome n=1

Continued: Adverse events by device part and category (Bellamkonda et al., 2021)	
Adverse events related to the stimulation lead	
Intra- and postoperative complications	35 p. (model 4063); most frequent complications: infection 8 p., lead wire protrusion from wound 5 p., traction 4 p., vein damage intraoperatively requiring additional incisions 4 p., lead too superficially placed 3 p.; other 10 complications: 11 p. (1 complication 2 p., 9 complications 1 p.)
Revision surgery	n=10 (model 4063); complications: lead too superficially placed n=3, traction n=3, lead wire protrusion from wound n=2, improper lead routing causing tethering n=1, infection n=1
Device explant	n=3 (model 4063); complications: infection n=1, lead erosion n=1, lead wire protrusion from the wound n=1
Adverse events in connection with the sensing lead	
Intra- and postoperative complications	26 p. (model 4323); complications: pneumothorax 5 p., infection 4 p., lead insulation damage 4 p., pain 4 p., lead migration to pleural space n=2; other 7 complications 1 p. each
Revision surgery	n=10 (model 4323); complications: lead insulation damage n=5, pain n=3, traction n=1, abnormal impedance values n=1
Device explant	n=2 (model 4323); complication: infection n=2

Appendix 2: Search strategies

Search strategy Medline via PubMed (last updated 09/19/2021)

Search	Query	Items	Time
31	#9 AND #30	707	02:20:08
30	#15 AND #29	2,127	02:20:01
29	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR	107,752	02:19:54
28	apnex	24	02:19:44
27	imthera	19	02:19:38
26	nyxoah	23	02:19:32
25	"inspire medical"	85	02:19:27
24	implantable neurostimulator [MeSH Terms].	12,5	02:19:21
23	electric stimulation therapy [MeSH Terms]	85,505	02:19:15
22	neuro-stimul*	140	02:19:09
21	neurostimul*	4,951	02:19:03
20	HNS[Title/Abstract]	2,238	02:18:58
19	HGNS	136	02:18:51
18	hypogloss* stimul*	1,22	02:18:46
17	UAS	3,407	02:18:40
16	upper airway stimul*	1,668	02:18:35
15	#10 OR #11 OR #12 OR #13 OR #14	26,443	02:18:28
14	Hypoglossal Nerve[Mesh.]	3,325	02:18:22
13	tongue muscle	6,589	02:18:15
12	geniogloss*	1,263	02:18:09
11	hypogloss* nerve	5,724	02:18:03
10	"upper airway"	15,17	02:17:56
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	52,876	02:17:48
8	Sleep Apnea, Obstructive[Mesh.]	23,282	02:17:41
7	sleep apnea syndromes[Mesh.]	38,647	02:17:33
6	snoring[Mesh]	4,377	02:17:27
5	snoring	8,237	02:17:20
4	OSAS	4,556	02:17:10
3	OSA	16,774	02:17:04
2	(sleep apnea) AND syndrome	28,067	02:16:59
1	obstructive sleep apnea	37,077	02:16:51

Search Strategy Cochrane Library (last updated 09/19/2021)

ID	Search	Hits
#1	obstructive sleep apn?ea	5881
#2	sleep apn?ea syndrome*	3204
#3	OSA	3483
#4	OSAS	671
#5	snore*	213
#6	snoring	899
#7	MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees	2092
#8	MeSH descriptor: [Snoring] explode all trees	209
#9	MeSH descriptor: [Sleep Apnea Syndromes] explode all trees	2795
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	7621
#11	upper NEAR/2 airway	1525
#12	hypogloss* NEAR nerve*	58
#13	geniogloss*	85
#14	tongue NEAR muscle*	136
#15	MeSH descriptor: [Hypoglossal Nerve] explode all trees	11
#16	#11 OR #12 OR #13 OR #14 OR #15	1695
#17	upper NEAR airway stimul*	196
#18	UAS	205
#19	hypogloss* stimul*	44
#20	HGNS	8
#21	(hns):ti,ab,kw	91
#22	neurostimul*	1024
#23	neuro-stimul*	37
#24	MeSH descriptor: [Electric Stimulation Therapy] explode all trees	7431
#25	MeSH descriptor: [Implantable Neurostimulators] explode all trees	188
#26	apnex	5
#27	inspire medical	9
#28	nyxoah	2
#29	imthera	3
#30	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	8908
#31	#16 AND #30	216
#32	#10 AND #31	128

The 128 "hits" are composed of:

105 "Cochrane trials”
(included in the systematic literature selection according to the research question)

6 "Cochrane review protocols"

17 "Cochrane reviews"