EUnetHTA JA3 WP4 - Other technologies, OTCA 21
External review by external experts and fact-check by manufacturers of the 2nd draft assessment on Hypoglossal Nerve Stimulation systems for treatment of Obstructive Sleep Apnea

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External expert					
Summary					
Marina Carrasco Llatas. Sociedad Española de Otorrinolaringología y Cirugía de cabeza y Cuello; Sección de Trastornos Respiratorios del Sueño. Servicio de Otorrinolaringología. Hospital Universitario Dr. Peset. Valencia	8	6	The use of HNS is more	3	Modified as suggested, thank you.
Marina Carrasco Llatas.	8	15-16	PSG is the gold standard diagnostic method, but probably the standard way to diagnose it due to the more avaliability it's the home polygraphy	2	Modified as suggested, thank you
Marina Carrasco Llatas.	8	14	The inadecuate tone of the UA muscles is not the only mechanism	1	Modified as suggested, thank you. A clarification is added.
Marina Carrasco Llatas.	8	26-31	An alternative for SOME of those patients is HNS (others have to go for other type of surgery, maxilofacial or soft tissue) WE don't remove uvulas or soft palates, I suggest you change it for	1	Modified as suggested, thank you. "Conventional surgery of the palate

Please add extra rows as needed.

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			conventional surgery of the palate or the tongue, it's more inclusive to all the procedures that we can do. And maxillofacial surgery of the bone is the best treatment for others with bone deficiences, besides the acceptance of the patients is not very low, I believe that the acceptance of my patients is high, they want surgery because they need a solution.		and tongue" is added.
Scope					
Marina Carrasco Llatas.	12	Comparison	The ref 4 is not updated, after this publications there have been published at least 2 RCT showing that tonsillectomy plus pharyngoplasty are better than nothing in non CPAP-compliant patients. 1. Joar S, Danielle F, Johan B, Arne L, Roberta N, Nanna B. Sleep quality after modified uvulopalatopharyngoplasty: Results from the SKUP3 randomized controlled trial. Sleep [Internet]. 2018 Jan 1 [cited 2018 Mar 3];41(1):1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29099950 1. Browaldh N, Bring J, Friberg D. SKUP3: 6 and 24 months follow-up of changes in respiration and sleepiness after modified UPPP. Laryngoscope [Internet]. 2018 Sep 1 [cited 2017 Dec 1];128(5):1238–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28862334 1. Fehrm J, Friberg D, Bring J, Browaldh N. Blood pressure after modified uvulopalatopharyngoplasty: results from the SKUP3randomized controlled trial. Sleep Med [Internet]. 2017 Jun [cited 2018 Mar 4];34:156–61. Available from:	1	Thank you for your comment. At present, no prospective evidence comparing invasive surgery and HGNS is available. The criteria not to consider surgery as an appropriate comparator to HGNS is maintained.

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			http://linkinghub.elsevier.com/retrieve/pii/S1389945717301570 1. Browaldh N, Bring J, Friberg D. SKUP 3 RCT; continuous study: Changes in sleepiness and quality of life after modified UPPP. Laryngoscope [Internet]. 2016;126(6):1484–91. Available from: http://doi.wiley.com/10.1002/lary.25642 1. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. Thorax [Internet]. 2013 Sep [cited 2014 Dec 14];68(9):846–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23644225 1. Sommer JU, Heiser C, Gahleitner C, Herr RM, Hörmann K, Maurer JT, et al. Tonsillectomy with Uvulopalatopharyngoplasty in Obstructive Sleep Apnea. Dtsch Arztebl Int. 2016;113:1–8. Ref 5 is not accesible to be sure on what they are funding this.		
Description and technical characteristics of the technology					
Marina Carrasco Llatas.	21	15-17	This is an oversimplification of the problem of OSA, it's not just the lack of tone, everybody has a lack of tone while sleeping and not everybody has OSA. Other factors are necessary to have OSA. If you've read reference 24 you must know. If it was just the muscle tone, everybody should have an implant, and everybody would be a success. You should reflect a little better the complexity of this issue.	1	Thank you for your comment. A clarification is added.

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Marina Carrasco Llatas.	22	1 - 8	The sensor doesn't detect alterations in the breathing pattern, it detects the breathing pattern so the stimulation is synchronized with the inspiration Not all the systems have a sensor to synchronize with inspiration, that's only in the inspire system. As inspire synchronizes with inspiration ONLY protrusor branches of the HNS are the ones stimulated, therefore is a selective stimulation. The Imthera system doesn't have a sensor and it stimulates both protrusor and retrusor branches of the HNS. What it's common to all the systems is that they keep the UA open	1	Thank you for your comment. Changes needed are made.
Marina Carrasco Llatas.	22	31	The other implants only stimulate protrusor muscles, I would not say the biggest one	2	Thank you for your comment. Changes needed are made.
Marina Carrasco Llatas.	22	36	I'm not sure that Nyxoah can monitor the tongue muscle, it stimulates all the time during inspiration because it's coordinated with time with respiration, it's on a certain time and off a certain time in each inspiration regardless the UA is obstructed or not (not all the breaths in the OSA are obstructed)	2	Thank you for your comment. Changes needed are added.
Marina Carrasco Llatas.	24	21	The absence of CCC on DISE is only mandatory for the inspire, but not for the imthera system	2	Thank you for your comment. A clarification is added.
Marina Carrasco Llatas.	26	2	In OSA surgery there are surgeries considered as minimal invasive, such as radiofrequency or palatal stiffening, these surgeries are performed in mild OSA as they are minimally effective, surgeries considered conventional surgeries include palatopharyngeal surgery (classical UPPP and the new pharyngoplasties that are more commonly performed in the last years worldwide) or tongue base surgery (either suspension, or resection techniques or whatever) LAUP is the only surgery that is not suggested to perform according to the AASM and the ISSS because it's results are not better, can be worse and has more morbidity, so the blue cross is wrong here. Please call me if you need any assistance or guidance related to surgery, some concepts are	1	Thank you for your comment. A clarification is added accordingly.

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			wrong and difficult to understand if you're not use to them, even better if it's in Spanish		
Marina Carrasco Llatas.	26	6	As classical UPPP is not the preferred technique nowadays, instead all the new pharyngoplasties are being used, in these techniques tissue removal is not so important, instead there's a muscle remodelation so the pharynx is not so collapsible with less side effects, see this article 1. Li HY, Lee LA, Hsin LJ, Fang TJ, Lin WN, Chen HC, et al. Intrapharyngeal surgery with integrated treatment for obstructive sleep apnea. Biomed J. 2019;42(2):84–92. I would rephrase this sentence so it's more in accordance with today's surgery, after all, HNS is performed in centers with huge experience on sleep surgery where the classical UPPP with the concept remove as much as possible does not longer exist.	1	Thank you for your comment. Text is rewritten accordingly.
Marina Carrasco Llatas.	26	10	UPPP has modest success in unselected patients, in selected patients has more than 80% of success see this article 1. Rotenberg BW, Theriault J, Gottesman S. Redefining the timing of surgery for obstructive sleep apnea in anatomically favorable patients. Laryngoscope [Internet]. 2014 Sep [cited 2014 Sep 28];124 Suppl:S1-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24737140	1	Thank you for your comment. Text is modified accordingly.
Marina Carrasco Llatas.	26	29	It's BiPAP no BPAP	3	Modified as suggested, thank you.
Marina Carrasco Llatas.	27	18	I would delete (sleep certified pulmonologist) any person with a sleep certificate who can read PSG can titrate HNG with training, in Germany are the ENTs in many centers the ones doing it, so try to be inclusive to all the specialties that can titrate	3	Modified as suggested, thank you.

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Marina Carrasco Llatas.	27	22-24	Tonsillectomy and nasal surgeries are the first surgeries that any ENT resident learns how to do in every country because they are the most prevalent problems in the ENT area, so don't trust those publications that say that are only performed in a limited number of ENT clinics, in fact nasal surgery can improve CPAP compliance, so it's very commonly performed despite its low impact in the AHI, but also increases QoL 1. Camacho M, Riaz M, Capasso R, Ruoff CM, Guilleminault C, Kushida CA, et al. The effect of nasal surgery on continuous positive airway pressure device use and therapeutic treatment pressures: a systematic review and meta-analysis. Sleep [Internet]. 2015 Jan 17 [cited 2015 Feb 8];38(2):279–86. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4288609&tool=pmcentrez&rendertype=abstract	2	Thank you for your comment. A clarification is added accordingly.
Health problem and current use					
Marina Carrasco Llatas.	31	1	In Spain severe OSA in Children is considered when AHI >10 1. Luz Alonso-Álvarez M, Canet T, Cubell-Alarco M, Estivill E, Fernández-Julián E, Gozal D, et al. Documento de consenso del síndrome de apneas-hipopneas durante el sueño en niños (versión completa). Arch Bronconeumol [Internet]. 2011 Jan [cited 2019 Feb 4];47:2–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22682520	1	Thank you for your comment. A clarification is added.

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Marina Carrasco Llatas.	32	13-19	The OoL questionnaires only can improve if the patient is treated, in this paragraph this is not clear that patients were treated, besides all the ref are improvements after HNS, all those questionnaires also improve after CPAP therapy	2	Thank you for your comment. A clarification is added.
Marina Carrasco Llatas.	34	25	I would add polygraphy as well, as many physicians are diagnosing OSA with type 3 sleep studies according to the guidelines	3	Thank you for your comment. A clarification is added.
Marina Carrasco Llatas.	34	43	I would delete soft palatal implants as Medtronic does not longer sell them	3	Modified as suggested, thank you.
Marina Carrasco Llatas.	38	17	I'm not a maxillofacial surgeon, just an ENT but prosthetic implants are not going to open the airway, they just change cosmetic, but cannot open the airway		Thank you for your comment. Text is maintained.
Marina Carrasco Llatas.	38	19	Complete excision of the inferior turbinate produces the empty nose syndrome and should be avoided as a general concept	2	Thank you for your comment. Changes needed are made.
Marina Carrasco Llatas.	38	4	Uvulopalatopharyngoplasty is not correct if you're talking about nose surgery or tongue surgery or bone surgery. Difficult to unite all those surgeries under one name. Usually we talk about soft tissue surgeries and bone surgeries, in case it's helpful.	1	Thank you for your comment. Text is rewritten in order to clarify.
Marina Carrasco Llatas.	40	22	Table 4-2 The Netherlands, it's DISE not OISE, ECRI it's BiPAP not BPAP	3	Modified as suggested, thank you.
Clinical effectiveness					
Marina Carrasco Llatas.	43	38	Actually, the p value in this article was 0.04: significant, so change it accordingly	1	Modified as suggested, thank you
Marina Carrasco Llatas.	44	14	NGNS is in OFF mode while awake, therefore it shouldn't affect daily life activities, maybe you should mention this	2	Thank you for your comment. Since this specific variable is not evaluated in the selected study, no evidence was found to answer this research question.
Marina Carrasco Llatas.	44	18	If HGNS is improving QoL and improving sleepiness, how is this not something that affects generic health-related QoL? Bad sleep affects to all the areas and functions of the body,	1	Thank you for your comment. Since this specific variable is not evaluated

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			people are more tired, depressed, and they don't even notice it, they get used to this, improving sleep improves many areas, If you want to learn more about sleep and how it affects to your body, health and everything read the book Why we sleep by Matthew Walker, it's impressive		in the selected study, no evidence was found to answer this research question.
Safety					
Marina Carrasco Llatas.	54	5	In the study by Woodson how can intention to treat approach can be done? There's no change in the group, so this cannot apply, why should something that cannot apply help to rate less? Ok that randomization is not explained, rate less, ok with blinding, although I can assure you that if you don't turn it on, or even if you turn it on but there's no stimulation, with such a big change in sleepiness and all that the patients are going to know so the blinding is not effective, but intention to treat does not apply here as there's no deviation from the initial plan, results are the same. This cannot make this study worse. You're the expert in rating studies, so tell us which kind of study we should perform so you think that the evidence is high and HGNS is useful. I'm sure that everybody that is implanting and watching how this therapy is helping to the patients will like to do it so this technology is spread and accepted without questions.	1	Thank you for your comment. Intention-to-treat analysis is a comparison of the treatment groups that includes all patients as originally allocated after randomization. Per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated. If done alone, this analysis leads to bias. The selected RCT by Woodson el al., presents a selection bias as only responders to UAS system from the STAR cohort were randomized. Likewise, the authors did not report a specific statement on the analysis approach for the missing observations which is required to evaluate the quality of RCT according to RoB 2 questionnaire.
Marina Carrasco Llatas.	55	11	In the study by Woodson et al the device was disconnected for 1 week, after the off period patients switched it on and returned to normal as soon as they switch the device on, this is	1	Thank you for your comment. A clarification is added accordingly as follows: "At 18 months, with therapy

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			what's good about this therapy and bad at the same time, you depend on switching it on, therefore compliance. As soon as the device is on the patients return to normal range values, the way you express normal range values returned at 18 months might lead to a wrong impression that after switching it off patients have no results after 18 months. I would say that normal range values kept in normal range at 18 months in both groups or something that cannot be mistaken.		ON in both groups, outcome measures had returned to normal range."
Marina Carrasco Llatas.	58	8	As I said before, hypoxemia time was better, you put 0.4 but it was 0.04	1	Thank you for your comment. A clarification is added accordingly
Appendix					
Marina Carrasco Llatas.	87		BiPAP	3	Modified as suggested, thank you.
Manufacturers					
Inspire Medical	2	14	The External Experts consulted for this rapid assessment include no European high volume users of this therapy (HGNS has not fully launched in Spain – the most experienced users of the therapy are in Germany, followed by the Netherlands and Belgium). Although the Spanish clinicians for whom the HTA agency sought opionon are excellent physicians, they have extremely limited experience with this therapy compared to others across the EU. Inspire recommended EUnetHTA contact the most experienced and published physicians, specifically, Prof. Joachim Maurer, Mannheim, Germany; Prof. Clemens Heiser, Munich, Germany; Prof. Armin Steffen, Luebeck, Germany; Prof. Nico DeVries, Amsterdam, Netherlands; Prof. Olivier Vanderveken, Antwerp, Belgium. Inclusion of perspective from these clinical experts may have prevented the scientific flaws in assessing the clinical evidence for HGNS which will be commented on below.	1	Thank you for your comment. This comment is outside of the scope of the factual accuracy check. The selection of external experts was assessed when the Project Plan was shared and consulted with all stakeholders, including manufacturers.

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Summary					
Inspire Medical	9	6-11	The assessment of available evidence states that there were no studies of device safety, and that all studies with the exception of the „unique comparative study" were prospective single arm studies. This is an incorrect conclusion. Focusing on the device for which there is high quality published evidence, i.e., the Inspire device, this statement is factually incorrect. As shown in the PICO, the comparator for HGNS is „No Therapy". As such, the STAR study in total is an RCT with 100% randomization to both „No Therapy" and „Therapy" as measured by the patient's baseline OSA and compared to the same patient's Therapy OSA. The nested randomization sub-study in the STAR trial (the „unique comparative study" mentioned in the report) was intended only as a validation that the outcomes of interest (reduction in Apnea Hypopnea Index, reduction in Oxygen Desaturation Index, and improvements in Quality of Life as measured by ESS and FOSQ), and percentage of sleep time with oxygen saturation less than 90%) were indeed a result of the therapy and not a placebo effect. Throughout this assessment, there is repeated scientific mis-representation of the STAR study design and randomized sub-study. We recommend this conclusion be modified to include safety outcomes from the STAR study, Strollo, et. Al, 2014 New England Journal of Medicine.	1	Thank you for your comment. This comment is outside of the scope of the factual accuracy check. The Project Plan stablished the study design required for effectiveness and for saferty assessment. The mentioned study by Strollo et al. 2014 is a multicenter, prospective, single-group, cohort design, can not be considered for the effectiveness assessment. The text is rewritten to clarify as follows: "Only one comparative study aimed at assessing effectiveness was identified. That study reported data on effectiveness but not on safety."
Inspire Medical	9	12	The draft HTA has inappropriately used the nested RCT sub-study from the Inspire STAR trial as the only study included in the assessment. The safety and efficacy of the Inspire HGNS system is well studied, and of sufficient quality to not only warrant CE Mark and FDA approval, but has been thoroughly studied and published on in other post-approval studies such as the ADHERE global registry which has current publication of over 1000 patients to date. In summary, the safety and efficacy of the Inspire HGNS system is published in the 2014 New England Journal of Medicine publication, Upper-airway stimulation for obstructive sleep apnea.	1	Thank you for your comment. This comment is outside of the scope of the factual accuracy check. The Project Plan stablished the study design required for effectiveness and

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			Strollo PJ et al. N Engl J Med. 2014 Jan 9; 370(2):139-49. It is scientifically inappropriate to include the STAR randomized controlled Withdrawal sub-study (Woodson, et. al, 2014 – Randomized Controlled Withdrawal Study of Upper Airway Stimulation on OA) in the health technology assessment without considering and including in the analysis the published results from the broader STAR study within which the sub-study was nested (Strollo et. al, 2014 NEJM).		for saferty assessment. The mentioned study by Strollo et al. 2014 is a multicenter, prospective, single-group, cohort design, can not be considered for the effectiveness assessment
Inspire Medical	9	17	The statement that a „selection bias" appears in the nested RCT is factually incorrect. The stated purpose of the comparative sub-study was to determine whether the „response" those patients who „responded" to the therapy per SHER criteria was an effect of the therapy, or placebo. As such, the inclusion criteria for the sub-study, by definitiion, had to be only those patients with positive response. It is recommended to remove the selection bias statement from the HTA.	1	Thank you for your comment. This comment is outside of the scope of the factual accuracy check. Regarding the selection bias in the referred study, information can be found on the discussion section of the original paper by Woodson et al. Pag 7: "Limitation of the study are the selection bias of only including responders to UAS therapy".
Inspire Medical	9	23	The HTA finds „no significant difference in Hyypoxemia Time...". This is factually incorrect. The comparator for HGNS in the document PICO for this assessment is „No Treatment" i.e. „no Therapy". Unfortunately, the assessers only included a small sub-study of the STAR study rather than including all outcomes and safety measures from the comprehensive STAR star	1	Thank you for your comment. This comment is outside of the scope of the factual accuracy check.

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			study (Strollo, et. Al, New England Journal of Medicine, 2014). The published results for the Secondary Outcome Measure of „percentage of sleep time with oxygen saturation <90%" is documented in Table 2 of the NEJM publication. There is a statistically significant difference between the comparator (Patient baseline where there is „no therapy") and the treatment at 12 months. The respective rates are: • Baseline – No Therapy: 8.7± 10.2 • Therapy Cohort @ 12 months: 5.9 ± 12.4 • Statistically significant p value of 0.01 In summary, the STAR substudy which randomized patients to a week of therapy „off" comparing to some patients who are randomized to keep therapy „on" to test for placebo effect, was not intended to be the comprehensive publication of study endpoints or safety measures. One must include the comprehensive STAR trial which is shows comparative results for 100% of the enrolled patients – the comparason (as described in the EUnetHTA PICO) being: No Therapy (the patient's baseline) vs. Hypoglossal Nerve Stimulation effect at 12 months.1		However, the *P* value of 0.4, initially indicated in the draft provided to you, was mistaken. Text is rewritten and clarified accordingly as follows: Significant differences were also found in Hypoxemia Time (percentage total sleep time with oxygen saturation < 90%). When the device was disconnected, the mean difference of change between ON-OFF was of 5.4 (0.1, 10.7 CI 95%, *P* value 0.04).
Inspire Medical	9	30	This is the most important point of feedback on scientific methodology for the HTA: On December 17, 2019, Inspire Medical Systems received communication from EUnetHTA including a Project Plan (*Project ID: OTCA21).* This project plan included a PICO framework by which this HTA would be performed. The „O"utcomes of interest, which were directly aligned with the intended application of HGNS for patients with moderate to severe obstructive sleep apnea, and for whom CPAP and other non-invasive therapies did not work, were the following (see page 10, section 2.2.2 Project Scope): • Aponea-Hypopnoea Index (AHI) • Oxygen Desaturation Index (ODI) • Epworth Sleepiness Scale (ESS) • Percentage of sleep time with the oxygen desaturation level below 90% • Quality of life (Functional Outcomes of Slee Questionnaire: FOSQ)	1	Thank you for your comment. This comment is outside of the scope of the factual accuracy check. The assessment team decided to modify some outcomes included originally in the draft Project Plan. As it was published, the effectiveness outcomes rate of cardiovascular events and rate of cerebrovascular evets were included in the final

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			• Technical and Procedural Success • Rate of Complications • Overall Mortality • Procedure -related complications • Device-related adverse events • Other adverse events The first issue at hand is the includion of „critical outcomes" that were not part of the documented PICO, such as cardio/cerebrovascular morbidity. Cardio/cerebrovascular morbidity and long-term effects in quality of life were not studied for this therapy by any manufacturer as the intention of the therapy is to improve the patient's current condition related to their untreated/undertreated OSA. It is well documented that improving a patient's sleep quality and increasing overall daily oxygenation will likely lead to long term cardiovascular improvement, however, such a study must be designed with a follow-up time of over 15 years to statistically prove this is true. HGNS therapy is clinically proven (in multiple peer-reviewed publications) to significantly improve the patients Obstructive Sleep Apnea condition as well as to significantly improve the patient's daytime sleepliness and overall quality of life. It is not claimed to be a long term solution for mortality improvement nor for cardiac mortality/morbidity. The second issue is that the methodologic flaw of considering only the Woodson, et. Al, RCT sub-study of the STAR trial rather than the comprehensive STAR trial leads EUnetHTA to the conclusion that there is no evidence of device or procedural related mortality, and later in the assessment, the claim that there is no safety or efficacy evidence. This is incorrect. Each of these endpoints are thoroughly discussed in the New England Journal of Medicine article (Strollo, et. Al, 2014 Upper-Airway Stimulation for Obstructive Sleep Apnea). We recommend inclusion of the endpoints documented in the 2014 Strollo, et. Al NEJM publicatioin in the HTA.		Project Plan.
Inspire Medical	9	38	The calculation of rate of patient Serious Adverse Events is scientifically unclear. The rate of	1	Thank you for your comment.

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			Serious Adverse Events (SAE) is reported in the STAR study for the Inspire therapy solution the New England Journal of Medicine article (Strollo, et. Al, 2014). There were two serious adverse events out of 126 patient implants related to the procedure and/or device, which equates to a SAE rate of 1.6%. All other SAEs (n=33) were adjudicated by the independent Adverse Event Committee, and were determined to be unrelated to the implantation procedure or implanted device. Given the poor quality of evidence from other HGNS technologies, it is scientifically inappropriate to combine SAEs from disparate therapy solutions and low quality published outcomes. We recommend changing the SAE rate to 1.6% and highlight that this SAE rate can only be expected with the Inspire device.		This comment is outside of the scope of the factual accuracy check. Regarding the frequency and severity of adverse events, information can be found on the Safety section of the document, table 6-1.
LIVN	10	23	THN3 study should appear as listed on clinicaltrials.gov	1	Thank you for your comment. Modified as suggested. .
Inspire Medical	11	Table 0-1	This table is labled as „HGNS Effectiveness", yet was drawn from data of a sub-study not intended to review effectiveness, rather was intended to prove that positive outcomes in patients who received theraputic benefit were derrived from HGNS therapy rather than placebo effect. The complete, comprehensive STAR study published in the NEJM in 2014 (Strollo, et. Al) is the source of effectiveness data for Inspire's HGNS data. Table 0-1 should be replaced with Table 2 of the NEJM peer reviewed publication. It is a scientific misnomer to imply that outcome measures from a sub-study not designed to review safety and effectiveness somehow represents the true safety and effectiveness for the comprehensive study at large.	1	Thank you for your comment. This comment is outside of the scope of the factual accuracy check.
Scope					
Inspire Medical	Section 1	SCOPE – PICO	We have strong objection to the inclusion of certain Outcomes in the PICO table that were not part of the PICO shared with stakeholders in the December 2019 publication (*Project*	1	Thank you for your comment. This comment is outside of the scope

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			ID: OTCA21). As stated earlier, the inclusion of Cardiovascular Events and Cerebrovascular Events are not relevant to the therapy in assessment. HGNS therapy is designed and studied to show improvement in OSA and Quality of Life related to Sleep. It is scientifically unsound to assign ultra-long range outcome measures that were not required by Regulatory bodies for proof of safety and effectiveness of this therapy solution (i.e. – CE Certification and FDA approval). Again, it is highly likely that improvement in sleep and oxygen saturation levels will improve long term mortality and cardiac functioin, but these outcomes are not relevant to the HGNS therapy. Patients suffering from OSA are sick and have a poor quality of life in the immediate timeframe. Treatment with HGNS has been clinically proven to safely and effectively significantly improve both OSA measures as well as quality of life.		of the factual accuracy check. The assessment team decided to modify some outcomes included originally in the draft Project Plan. As it was published, the effectiveness outcomes rate of cardiovascular events and rate of cerebrovascular evets were included in the final Project Plan.
Description and technical characteristics of the technology					
LIVN	21	29	This is the exclusive mode of action of the Inspire therapy. LivaNova's aura6000 or Nyxoah's Genio therapies do not require a sensor.	1	Thank you for your comment. Modified as suggested.
LIVN	22	3	There are no wearable controllers for neither of the therapies. Inspire UAS, LivaNova aura6000 are fully implanted systems controlled by an external remote control. Nyxoah's Genio is partially implanted with an external battery and NO external control	1	Modified as suggested, thank you.
LIVN	22	26	Implant-ed => implanted		Modified as suggested, thank you.
LIVN	22	31	The Genioglossus (GG) is not the tongue's largest muscle. The GG is responsible for the protrusion of the tongue, and protrusion of the tongue has been found to dilate the airway.This is however not the mode of action of the aura6000 therapy which aims at preserving/restoring general muscle tone.	1	Modified as suggested, thank you.
LIVN	22	33	Nyxoah's currently CE marked technology is the Genio therapy, not the SAT (visit www.nyxoah.com)	1	Modified as suggested, thank you.
LIVN	22	35	The statement "A fundamental difference to other neurostimulation devices is that the Nyxoah	1	Modified as suggested, thank you.

Please add extra rows as needed.

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			SAT system can monitor the tongue and stimulate the muscles only when it blocks the airway" is incorrect. The Genio device delivers trains of stimulation impulsions based on a predetermined duty cycle. See the description of the device in "Bilateral Hypoglossal Nerve Stimulation for Treatment of Adult Obstructive Sleep Apnea" (https://doi.org/10.1183/13993003.01320-2019)		
LIVN	22	40	The Genio does not have a remote	2	Modified as suggested, thank you.
LIVN	22	42	There appears to be a misunderstanding here: the purpose of the remote for Inspire UAS and aura6000 is to start and stop the therapy. For the aura6000, the remote also has a charging function as the battery inside the IPG is rechargeable	2	Modified as suggested, thank you.
LIVN	23	1	In table, line "Stimulation lead", authors need to understand the fundamental differences in the electrodes of the Inspire UAS and aura6000 THN therapies: in Inspire UAS, the polarity of the electrodes has to be determined, so that there is in the end only one anode and one cathode. For the aura6000, all 6 electrodes are cathodes, the anode being the case of the implant. This allows for a greater number of therapeutic possibilities than the Inspire UAS.	1	Thank you for your comment. A clarification is added accordingly.
LIVN	23	4	This procedure is only valid for Inspire UAS and aura6000 therapies	1	Modified as suggested, thank you.
LIVN	23	7	It is mentioned twice in this line "sensing leads". There is only one sensing lead in the Inspire UAS therapy, and none on the aura6000	1	Modified as suggested, thank you.
LIVN	24	12	Why are you representing only the Inspire UAS therapy?	1	Thank you for your comment. Changes needed are made.
LIVN	24	14-16	The English language is grammatically incorrect. One could say that "As a conclusion, the Hypoglossal nerve stimulation (HGNS) has emerged as an alternative approach based on upper-airway stimulation [30] in moderate to severe OSAS patients who fail CPAP"		Modified as suggested, thank you.
LIVN	24	16	It is important to say that not only the device is implanted under the skin in the chest but also in the neck, as this is where the electrodes go. The chest only hosts the IPG (aura6000, Inspire	2	Thank you for your comment. Changes needed are made.

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			UAS)		
LIVN	24	21-22	Complete concentric collapse on drug-induced sleep endoscopy and BMI<32 are exclusively related to Inspire UAS and Genio therapies. Aura6000 is not using drug-induced sleep endoscopy as a diagnostic tool (note: drug induced sleep endoscopy is not a reimbursed diagnostic method). Genio limits AHI to 60 and absence of positional OSA.	1	Thank you for your comment. Changes needed are made.
LIVN	25	11	Evicore is not a medical society, why should their recommendations be cited here?		Thank you for your comment. Changes needed are made.
LIVN	25	45	It is unclear what these 15-20% refer to. Those should be the ones candidates to conventional surgical procedures as listed further but without HGNS for which there is not sufficient evidence.		Thank you for your comment. Changes needed are made.
LIVN	26	47	Aura6000 has received 2 FDA IDE (THN2 & THN3)	1	Modified as suggested, thank you.
LIVN	27	3	PAP is not a procedure but a conservative therapy		Thank you for your comment. Changes needed are made.
LIVN	27	13	Drug induced sleep endoscopy is not a standard examination procedure and is not required for the aura6000	1	Thank you for your comment. Changes needed are made.
LIVN	27	20	This is true for all therapies (training is required prior use or prescription)	2	Modified as suggested, thank you.
LIVN	27	30	The therapies you are citing have little to none clinical evidence		Thank you for your comment. This comment is outside of the scope of the factual accuracy check. The text is maintained.
LIVN	27	41	Endoscopy unit is not required for aura6000	1	Modified as suggested, thank you.
LIVN	27	43	Unfortunately, "Generally" is not the case. Neither Genio nor aura6000 have these	1	Thank you for your comment.

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			characteristics.		Changes needed are made.
LIVN	27	45	Only aura6000 and Genio therapies have a charging unit.	2	Thank you for your comment. Changes needed are made.
LIVN	28	28	The table does not fairly present the same information for all therapies. In the case of the aura6000, the system battery life is of 12 to 15 years.	1	Thank you for your comment. Changes needed are made.
LIVN	28	17	The PMA limits Inspire UAS AHI to 55 (not 65)	1	Modified as suggested, thank you.
LIVN	29	13	The aura6000 therapy is available for sale in Germany, Austria, Spain, Portugal, Israel & Colombia under the CE label	1	Thank you for your comments. Changes needed are added.
LIVN	29	15	Aura6000 is only under investigation in the US, please make this clear.	1	Modified as suggested, thank you.
LIVN	29	24	HGNS is not reimbursed in the UK, it has NICE interventional procedure guidance recommended under ,special arrangements, this is not a reimbursement status.	1	Thank you for your comment. Changes needed are made.
LIVN	29	26	Inspire UAS is NOT reimbursed in France nor in Belgium (currently submitting application for reimbursement in France: https://www.has-sante.fr/jcms/p_3180452/fr/decision-n-2020-0086/dc/seesp-du-1er-avril-2020-du-college-de-la-haute-autorite-de-sante-constatant-l-absence-d-impact-significatif-du-produit-systeme-de-stimulation-des-voies-aeriennes-superieures-inspire-iv-sur-les-depenses-de-l-assurance-maladie The reference here to 'reimbursement' is for coverage with evidence development	1	Thank you for your comment. Changes needed are made.

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			schemes, this is not the same as national reimbursement.		
LIVN	29	31	Evicore is a commercial player that cannot be put at the same level as DGSM or the Dutch guidelines		Thank you for your comment. Changes needed are made.
Health problem and current use					
LIVN	32	43	Your analysis fails to cite "The price of fatigue: the surprising economic costs of unmanaged sleep apnea", a publication from Harvard Medical School available here: [1]		Thank you for your comment. This comment is outside of the scope of the factual accuracy check. The reference is not added.
LIVN	33	40	Evicore guidelines are not widely recognized		Thank you for your comment. Changes needed are made.
LIVN	35	6	The chart here represents the US guidelines. Significant variations exist in EU countries.		Thank you for your comment. A clarification on European situation is added.
LIVN	37	1	Query the relevance of the Evicore clinical guidelines		Thank you for your comment. Changes needed are made.
LIVN	38	4	This section should not be named Uvulopalatopharyngoplasty but "Upper airway surgeries", of which UPPP is one.		Thank you for your comment. Changes needed are made.
LIVN	39	1-7	You only cite chest as a surgical site, however the hypoglossal nerve is accessed in the neck, in the mandibular area (between the chin and the submandibular gland)	1	Thank you for your comment. Text is rewritten in order to clarify.
Clinical effectiveness					
LIVN	43	6	STAR does not have sham control (it has therapy withdrawal)		Modified as suggested, thank you.
Safety					

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LIVN	89	4	HGNS is not reimbursed in the UK, it has NICE interventional procedure guidance recommended under ,special arrangements, this is not a reimbursement status. Inspire UAS is NOT reimbursed in France nor in Belgium (currently submitting application for reimbursement in France: https://www.has-sante.fr/jcms/p_3180452/fr/decision-n-2020-0086/dc/seesp-du-1er-avril-2020-du-college-de-la-haute-autorite-de-sante-constatant-l-absence-d-impact-significatif-du-produit-systeme-de-stimulation-des-voies-aeriennes-superieures-inspire-iv-sur-les-depenses-de-l-assurance-maladie The reference here to 'reimbursement' is likely for coverage with evidence development schemes, this is not the same as national reimbursement.	1	Thank you for your comment. Changes needed are made.

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