NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Senza spinal cord stimulation system for delivering HF10 therapy to treat chronic neuropathic pain

EAC supplementary documents

The enclosed documents were produced during the course of the evaluation by 2 independent external assessment centres (EACs) to assist the NICE medical technologies advisory committee (MTAC) in making their recommendations:

1. **EAC advice on consultation comments [MTCD1]** – a document produced by the Newcastle and York External Assessment Centre in response to the comments NICE received during the first publication consultation on the draft guidance which took place in November 2017.
2. **EAC advice on consultation comments [MTCD2]** – a document produced by the Newcastle and York External Assessment Centre in response to the comments NICE received during the second publication consultation on the draft guidance which took place in April 2018.
3. **Errata to EAC advice on consultation comments** – a document produced by the Newcastle and York External Assessment Centre to correct factual inaccuracies in the above EAC advice documents, arising from consultee feedback.
4. **EAC evidence review** – a document produced by the King's Technology Evaluation Centre to assess concerns raised during the first public consultation around certain evidence considered by the committee.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

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Advice on Senza HF10 SCS consultation comments

Produced by Newcastle and York External Assessment Centre

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Executive Summary

Following the Medical Technologies Advisory Committee (MTAC) in September 2017, draft guidance and associated documents were made available for consultation for MT330 Senza Spinal Cord Stimulation (SCS) System for the treatment of chronic pain. Due to the large volume of responses received from stakeholders, and the identification of new clinical evidence not available at the time of writing of the Assessment Report, the Newcastle and York External Assessment Centre (EAC) has produced this advisory document, which has the aim of reviewing the new evidence and addressing uncertainties or criticisms made by consultees. Where possible, this document aligns with consultee comments.

Sixty six studies were identified by stakeholders as being potentially relevant to the guidance. The EAC assessed their relevance and compatibility with the final scope of the evaluation. Most studies (63) were excluded because they were not applicable; the intervention was incorrect (i.e. not Senza HF10 therapy); low patient numbers; or because they were conference abstracts. Three studies (Al-Kaisy *et al.*, De Andres *et al.*, and Van Buyten *et al.*, all published late 2017) were identified that were within scope, and these were reviewed.

The study by Al-Kaisy *et al.* (2017) reported extended follow up of a small case series that was included in the AR. It reported that the pain-relieving benefits of Senza HF10 therapy are maintained for at least 3 years. However, the population - patients naïve of surgery - though technically in scope, was not representative of most patients undergoing SCS. The study by De Andres *et al.* (2017) was an RCT that compared Senza HF10 with conventional rechargeable low frequency SCS over 1 year. Both technologies were associated with only modest improvements in overall pain reduction, and there was no significant difference reported between technology types. These results were not consistent with those reported in the SENZA-RCT, which was the key study that informed the AR. The study by Van Buyten *et al.* (2017) was a retrospective chart review (n = 955) that reported on the explantation rates for Senza HF10, conventional low frequency non-rechargeable SCS, and conventional low frequency rechargeable SCS. Overall, 180 implants (19%) were removed for unanticipated reasons category, of which 94 (10%) were due to inadequate pain relief. Rechargeable technologies had significantly higher explantation rates due to inadequate pain relief than conventional non-rechargeable SCS.

Regarding the clinical evidence, the EAC considered the study by De Andres *et al.* (2017) had important implications for the conclusions of the AR and, instead of there being unequivocal evidence in support of Senza HF10 therapy compared with conventional low frequency SCS, this evidence should now be described as equivocal, which adds uncertainty to the conclusions. Differences in the outcomes reported by the studies may have been due to several sources of potential bias identified by the EAC and consultees. The results from the RCT did not impact on the economic evidence, as degree of pain relief was not an input that affected the model outputs. Extrapolated data from the Van Buyten study, for unanticipated explantation of SCS device for any reason, suggested that conventional non-chargeable SCS may be an approximately cost neutral option compared with Senza HF10.

However, all estimates on the relative costs of Senza HF10 compared with low frequency SCS technologies are also subject to structural limitations of the model and uncertainty relating to its clinical and cost inputs.

Abbreviations

AiC	Academic in confidence
AR	(EAC) Assessment report
CGIC	Clinician Global Impression of Change
CI	Confidence interval
CiC	Commercial in confidence
CRPS	Complex regional pain syndrome
EAC	External Assessment Centre
EQ-5D	Euroqol 5 dimensions
FBSS	Failed back surgery syndrome
FNSS	Failed neck surgery syndrome
FU	Follow up
GAF	Global Assessment of Functioning
GCP	Good clinical practice
HF10	High frequency SCS therapy at 10kHz (Senza HF10TM technology)
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IPG	Implantable pulse generator
MRI	Magnetic Resonance Imaging
MTAC	Medical Technologies Advisory Committee
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRS	Numeric rating scale
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROMs	Patient reported outcome measures
PY	Person year
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SCS	Spinal cord stimulation
SD	Standard deviation
SF-36	Short form 36 item
VAS	Visual analogue scale

Section 1: Background

1.1 BACKGROUND TO DOCUMENT

Following the Medical Technologies Advisory Committee (MTAC) meeting on September 22nd 2017, draft guidance and associated documents were made available for consultation for MT330 Senza Spinal Cord Stimulation (SCS) System for the treatment of chronic pain. The Newcastle and York External Assessment Centre (EAC) and the National Institute for Health and Care Excellence (NICE) agreed that the preferred way of responding to consultee comments (which were large in volume) was to produce a supplementary advisory document and, where possible, fully respond to consultee comments by citing sections of this report. This document is complementary and additional to the original EAC assessment report (AR) produced by Willits *et al.* (2017) [1].

1.2 DOCUMENT STRUCTURE

The document is arranged as follows:

- Section 2 reviews the studies cited by stakeholders during the public consultation and identifies those which are considered relevant to the decision problem. Studies are only considered for inclusion in this advisory report if they are within the original scope as defined by population, intervention, comparator, outcomes (PICO) and study type. Other studies are briefly discussed if they are considered to provide background information pertinent to MTAC's decision making.
- Section 3 reports on the recent study by Van Buyten *et al.* (2017)
- Section 4 reports on the recent study by Al-Kaisy *et al.* (2017)
- Section 5 reports on the recent study by De Andres *et al.* (2017). Results from this study are compared with the SENZA RCT. Possible reasons for discrepancies are explored, and the implications of differences in results on previous conclusions made by the AR are discussed.
- Section 6 addresses characteristics of the technology that were commented upon during the public consultation. This includes a summary of additional information provided by the company regarding battery charging (commercial in confidence) and recent changes to the Magnetic Resonance Imaging (MRI) conditionality of the Senza device.
- Section 7 is concerned with costing and economic modelling. In this section, important limitations of the economic model, and the reasons for these, are briefly discussed. Sensitivity analysis informed by new clinical evidence is carried out. The impact of these changes on the AR conclusions is discussed.
- Section 8 reports a brief overview summarising the consultee considerations from the perspective of the EAC.

Section 2: Recently published and emerging evidence

2.1 INCLUDED AND EXCLUDED STUDIES

A full systematic literature search was performed by the EAC, and documented using the process described by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology [2], was reported in the AR [1]. This had a search date cut-off of June 2017.
During the course of the consultation, 66 studies were identified by stakeholders as being potentially relevant to the guidance, some of which have been published subsequent to the original systematic search date.

The EAC assessed the relevance of these 66 studies and compatibility with the final scope of this evaluation (MT330) [3]. Using this process, studies that would have been included, had they been identified at the literature search stage of the AR, were selected as recently published and emerging evidence for EAC review in this advisory report. Studies that would not have been included previously have been excluded, consistent with process. However, the EAC has not performed a further systematic literature search on material published since June 2017. Hence the studies identified in this advisory report are not exhaustive, and there is a possibility that other recent and emerging relevant studies, which were not cited by the stakeholders during the public consultation, are not included in this work.

The main reasons for exclusion were because the studies or reviews related to background information rather than the decision problem; because the intervention was not Senza HF10 therapy; low patient numbers; or because they were conference abstracts. Regarding the latter point, conference abstracts were excluded from the AR report because they lack internal validity, are not peer-reviewed, and are inadequately reported for appraisal. In addition, in the case of Senza HF10 therapy, the EAC could not be confident that the same patients were not reported in multiple abstracts and/or published studies (i.e. double counting of participants).

2.1.1 Included studies

The EAC considered that three studies would have been included had they been identified by the literature search in the original AR. These studies were all published subsequent to the literature search performed in the AR. Details of the studies are listed in Table 1. These studies are discussed in more depth in sections 3, 4 and 5.

Twelve studies that were previously included in the AR, or are addressed in this supplementary advisory report as studies of interest, are listed in Table 2.

The reasons for exclusion for the other 51 studies are summarised in Table 3.

Table 1. *Details of recent and emerging new clinical studies in scope of the assessment.*

Study reference (Follow up)	**Study type (Sample size)**	**Population and setting**	**Intervention and comparator**	**Outcomes**	**Comment**
Van Buyten (2017) [4] (5 years)	Retrospective chart review (n = 955)	Patients who have received an SCS implant. Includes pain of all types, but majority with neuropathic pain of back and legs. Three European centres.	I: HF 10kHz rechargeable SCS* C1: TLF rechargeable SCS C2: TLF non-rechargeable SCS	Explantation rate. Reasons for explantation. Battery life	Reason for implant removal was outcome in scope. Key comparative study that provides independent explantation data and reasons for explantation. Discussed in Section 3.
Al-Kaisy (2017) [5] (3 years, n = 17)	Prospective case series (n = 21)	Patients naïve to surgery with predominant back pain which was chronic and severe. Guy's hospital, UK.	I: Senza HF10 therapy C: None	Pain intensity using VAS. ODI. HRQoL (EQ-5D) SF-36 Global impression of change Patient satisfaction Opioid use Sleep quality Work status AE	Extended follow up of study included in AR [6](12 months follow up). Extensive reporting of outcomes. However, small sample size and no comparator. Discussed in Section 4.
De Andres (2017) [7] (1 year)	RCT (n = 55)	Patients with chronic, intractable pain of the trunk and/or limbs that has remained refractory to conservative therapy for at least six months	I: Senza HF10 therapy C: TLF rechargeable SCS (Surescan RestoreSensor, Medtronic)	Pain score (NRS) PD-Q ODI SF-12 Sleep scale HAD PGIC	This has comparable scope to the SENZA-RCT. Discussed in detail in Section 5.

Abbreviations: AE – adverse events; C – comparator; EQ-5D – Euroqol 5 dimensions; FBSS – failed back surgery syndrome; HAD - Hospital Anxiety and Depression ; HF – high frequency; HRQoL – health related quality of life; I –intervention; NRS – numeric rating scale; ODI - Oswestry Disability Index; PGIC – Patient Global impression of improvement; PD-Q - Pain Detect Questionnaire; RCT - randomised controlled trial; SCS – spinal cord stimulation; SF-36 – short form 36; TLF – traditional low frequency; VAS – visual analogue scale.

* Assumed to be Senza HF10 therapy

Table 2. *Studies cited by stakeholders which were already addressed in the AR [1], or are addressed in this advisory report as a study of interest.*

Themed Comment number(s)	**Study reference (as provided by the consultee)**	**Reason for exclusion against the original literature search scope**
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Annemans, L., Van Buyten, J. P., Smith, T., & Al-Kaisy, A. (2014). Cost effectiveness of a novel 10 kHz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS). J Long Term Eff Med Implants, 24(2-3), 173-183. Retrieved from http://www.dl.begellhouse.com/journals/1bef42082d7a0fdf,0134a0a71af442c9,63d1c2fa20ed74ea.html	Was economic / QoL study already in original Assessment Report (AR).
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Kapural, L., Yu, C., Doust, M. W., Gliner, B. E., Vallejo, R., Sitzman, B. T., . . . Burgher, A. H. (2015). Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology, 123(4), 851-860. doi:10.1097/aln.0000000000000774	Already in AR.
APPENDIX 1 References Comments 4, 7, 8, 34, 37, 65, 66, 84, 85, 91, 109, 110, 148	Perruchoud, C., Eldabe, S., Batterham, A. M., Madzinga, G., Brookes, M., Durrer, A., . . . Buchser, E. (2013). Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. Neuromodulation, 16(4), 363-369; discussion 369. doi:10.1111/ner.12027	Not in primary evidence but addressed in AR as sham study of interest.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Russo, M., Verrills, P., Mitchell, B., Salmon, J., Barnard, A., & Santarelli, D. (2016). High Frequency Spinal Cord Stimulation at 10 kHz for the Treatment of Chronic Pain: 6-Month Australian Clinical Experience. Pain Physician, 19(4), 267-280.	Already in AR.
APPENDIX 1 References Comments 5, 6, 7, 8, 12, 18, 37, 65, 66, 84, 85, 90, 91, 106, 109, 110, 148	Thomson, S. E. A. (2017). Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial. Neuromodulation (In press)	Not Senza device but addressed in this Advisory report as an additional study of interest (as Perruchoud et. al (2013) was in the AR).
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75, 143, 144, 156, 165, 166, 174	Taylor R S, Ryan J, O'Donnell R, Eldabe S, Kumar K and North R B 2010 The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome The Clinical journal of pain 26 463-9	Key study in NICE TA159, already addressed in AR.
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75,	Simpson E L, Duenas A, Holmes M W and Papaioannou D 2008 Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (Technology Assessment Report). (The University of Sheffield, School of Health and Related Research (ScHARR))	Key study in NICE TA159, already addressed in AR.

Themed Comment number(s)	Study reference (as provided by the consultee)	Reason for exclusion against the original literature search scope
143, 144, 156, 165, 166, 174		
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75, 143, 144, 156, 165, 166, 174	Kumar 2006 Kumar K, Wilson J R, Taylor R S and Gupta S 2006b Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact Journal of neurosurgery. Spine 5 191-203	Retrieved - this 2006 economic study of SCS complications was referenced in the ScHARR assessment report underpinning TA159, already addressed in AR.
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75, 143, 144, 156, 165, 166, 174	Rapcan R, Mlaka J, Venglarcik M, Vinklerova V, Gajdos M, Illes R. High-frequency-Spinal Cord Stimulation. Bratislavske lekarske listy. 2014;116(6):354-6.	Already in AR.
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75, 143, 144, 156, 165, 166, 174	North RB, Kidd DH, Olin J, Sieracki JM, Farrokhi F, Petrucci L, Cutchis PN (2005) Spinal cord stimulation for axial low back pain: a prospective, controlled trial comparing dual with single percutaneous electrodes. Spine (Phila Pa 1976) 30:1412–8.	Already in AR.
Comment 19	Al-Kaisy A, Palmisani S, Sanderson K, Tan Y, McCammon S. A randomized, sham-control, double blind, cross-over trial of sub-threshold spinal cord stimulation at various kilohertz frequencies (SCS Frequency Study). North American Neuromodulation Society Meeting, Las Vegas, US. December 2015. (In Press) Neuromodulation Journal. Full paper: Al-Kaisy et al (2018) Prospective, Randomized, Sham-control, Double Blind, Cross-over Trial of Sub-Threshold Spinal Cord Stimulation at Various Kilohertz Frequencies in Subjects Suffering from Failed Back Surgery Syndrome (SCS Frequency Study)	Copy of the full paper received from the consultee via NICE as Academic in Confidence (AiC). Excluded from primary evidence as not Senza device. Included in this Advisory report as a study of interest.
Comment 28	Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, *et al.* Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain. 2007 Nov;132(1-2):179-88	Already in AR.

Table 3. *Summary of 51 excluded studies from the stakeholder consultation comments.*

Themed Comment number(s)	**Study reference (as provided by the consultee)**	**Reason for exclusion against the original literature search scope**
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Berg, A. P., Mekel-Bobrov, N., Goldberg, E., Huynh, D., & Jain, R. (2017). Utilization of multiple spinal cord stimulation (SCS) waveforms in chronic pain patients. Expert Rev Med Devices, 14(8), 663-668. doi:10.1080/17434440.2017.1345621	Abstract reviewed: https://www.ncbi.nlm.nih.gov/pubmed/28662588 Wrong device (Boston Spectra) & multiple waveform intervention.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Bicket, M. C., Dunn, R. Y., & Ahmed, S. U. (2016). High-Frequency Spinal Cord Stimulation for Chronic Pain: Pre-Clinical Overview and Systematic Review of Controlled Trials. Pain Med, 17(12), 2326-2336. doi:10.1093/pm/pnw156	Was record 27 excluded at first Senza sift as Systematic Review (SR).
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	de Vos, C. C., Bom, M. J., Vanneste, S., Lenders, M. W., & de Ridder, D. (2014). Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation, 17(2), 152-159. doi:10.1111/ner.12116	Was record 136 excluded at first Senza sift (as wrong device).
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Deer, T. R., Mekhail, N., Provenzano, D., Pope, J., Krames, E., Leong, M., . . . North, R. (2014). The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation, 17(6), 515-550; discussion 550. doi:10.1111/ner.12208	Was record 139 excluded at first Senza sift as a Guideline.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Falowski, S. M., Celii, A., Sestokas, A. K., Schwartz, D. M., Matsumoto, C., & Sharan, A. (2011). Awake vs. asleep placement of spinal cord stimulators: a cohort analysis of complications associated with placement. Neuromodulation, 14(2), 130-134; discussion 134-135. doi:10.1111/j.1525-1403.2010.00319.x	Device(s) not specified, but retrospective review of implants from 2002-2007 pre-dates 2010 CE marking of Nevro Senza. The outcomes reported are also for an awake versus asleep technique of device placement.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Johanek JM, C. T., Vera-Portocarrero LP. (2014). Low and High Frequency Parameters Impact SCS Therapeutic Mechanisms. Retrieved from www.epostersonline.com/nans2014/node/103	EAC reviewed the abstract of this conference poster at: http://www.epostersonline.com/nans2014/node/103 Animal study - out of scope.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Sci Transl Med, 6(218), 218ra215. doi:10.1126/scitranslmed.3006175	A study of placebo effects of drug labelling information in migraine. Out of scope on population and Senza HF10 as device as opposed to drug therapy.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Kriek, N., Groeneweg, J. G., Stronks, D. L., de Ridder, D., & Huygen, F. J. (2017). Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and	Was record 10 excluded at first Senza sift (as wrong device and CRPS population).

Themed Comment number(s)	Study reference (as provided by the consultee)	Reason for exclusion against the original literature search scope
	placebo-controlled crossover trial. Eur J Pain, 21(3), 507-519. doi:10.1002/ejp.944	
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Kriek, N., Groeneweg, J. G., Stronks, D. L., & Huygen, F. J. (2015). Comparison of tonic spinal cord stimulation, high-frequency and burst stimulation in patients with complex regional pain syndrome: a double-blind, randomised placebo controlled trial. BMC Musculoskelet Disord, 16, 222. doi:10.1186/s12891-015-0650-y	Was record 99 excluded at first Senza sift (as wrong device and CRPS population).
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	North, J. M., Hong, K. J., & Cho, P. Y. (2016). Clinical Outcomes of 1 kHz Subperception Spinal Cord Stimulation in Implanted Patients With Failed Paresthesia-Based Stimulation: Results of a Prospective Randomized Controlled Trial. Neuromodulation, 19(7), 731-737. doi:10.1111/ner.12441	Was record 62 excluded at first Senza sift (as wrong device).
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Rutherford, B. R., & Roose, S. P. (2013). A model of placebo response in antidepressant clinical trials. Am J Psychiatry, 170(7), 723-733. doi:10.1176/appi.ajp.2012.12040474	EAC reviewed abstract at: https://www.ncbi.nlm.nih.gov/pubmed/23318413 A study of contributory factors to placebo response in antidepressant drug trials. Out of scope on population and Senza HF10 as device as opposed to drug therapy.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Schedlowski, M., Enck, P., Rief, W., & Bingel, U. (2015). Neuro-Bio-Behavioral Mechanisms of Placebo and Nocebo Responses: Implications for Clinical Trials and Clinical Practice. Pharmacol Rev, 67(3), 697-730. doi:10.1124/pr.114.009423	Full paper retrieved - Comprehensive review of placebo and nocebo effects, although inferences are for pharma, rather than device therapies. Out of scope of Senza assessment.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Song, Z., Viisanen, H., Meyerson, B. A., Pertovaara, A., & Linderoth, B. (2014). Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. Neuromodulation, 17(3), 226-234; discussion 234-225. doi:10.1111/ner.12161	Was record 159 excluded at first Senza sift (as animal study).
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Van Havenbergh, T., Vancamp, T., Van Looy, P., Vanneste, S., & De Ridder, D. (2015). Spinal cord stimulation for the treatment of chronic back pain patients: 500-Hz vs. 1000-Hz burst stimulation. Neuromodulation, 18(1), 9-12; discussion 12. doi:10.1111/ner.12252	Was record 129 excluded at first Senza sift (as wrong device).
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Veizi, E., Hayek, S. M., North, J., Brent Chafin, T., Yearwood, T. L., Raso, L., . . . Mekel-Bobrov, N. (2017). Spinal Cord Stimulation (SCS) with Anatomically Guided (3D) Neural Targeting Shows Superior Chronic Axial Low Back Pain Relief Compared to Traditional SCS-LUMINA Study. Pain Med, 18(8), 1534-1548. doi:10.1093/pm/pnw286	Full paper retrieved - Out of scope. Intervention is Boston Scientific Precision Spectra.
APPENDIX 1 References	Weimer, K., Colloca, L., & Enck, P. (2015). Placebo effects in psychiatry:	Abstract reviewed at:

Themed Comment number(s)	Study reference (as provided by the consultee)	Reason for exclusion against the original literature search scope
Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	mediators and moderators. Lancet Psychiatry, 2(3), 246-257. doi:10.1016/s2215-0366(14)00092-3	https://www.ncbi.nlm.nih.gov/pubmed/25815249 Wrong population: psychiatric disorders including: depression, schizophrenia, mania, attention-deficit hyperactivity disorder, autism, psychosis, binge-eating disorder, and addiction.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	Youn, Y., Smith, H., Morris, B., Argoff, C., & Pilitsis, J. G. (2015). The Effect of High-Frequency Stimulation on Sensory Thresholds in Chronic Pain Patients. Stereotact Funct Neurosurg, 93(5), 355-359. doi:10.1159/000438998	Record 130 excluded at second Senza sift as wrong device.
APPENDIX 1 References Comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110, 148	A. Koulousakis, G. Matis, G. Bara, A. Chatzikalfas and V. Visser-Vandewalle. 10 kHz and 1.2 kHz Comparison Concerning Clinical Outcomes and Charge Burden. http://epostersonline.com/nans2017/node/423	Poster abstract reviewed at: http://epostersonline.com/nans2017/node/423 Excluded on basis of wrong device (Precision Plus High Rate with Multiwave Technology (Boston Scientific, Valencia, CA, USA)) and being a case series of n=3 patients.
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75, 143, 144, 156, 165, 166, 174	Miller JP, Eldabe S, Buchser E, Johanek LM, Guan Y, Linderoth B (2016) Parameters of Spinal Cord Stimulation and Their Role in Electrical Charge Delivery: A Review. Neuromodulation 19:373–84.	Was record 55 excluded at first Senza sift (as review article, not Senza).
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75, 143, 144, 156, 165, 166, 174	Smith H, Youn Y, Pilitsis JG (2015) Successful use of high-frequency spinal cord stimulation following traditional treatment failure. Stereotact Funct Neurosurg 93:190–3.	Was record 127 excluded at first Senza sift (wrong device).
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75, 143, 144, 156, 165, 166, 174	Barolat G, Massaro F, He J, Zeme S, Ketcik B (1993) Mapping of sensory responses to epidural stimulation of the intraspinal neural structures in man. J Neurosurg 78:233–9.	Retrieved, but this study does not seem to have been cited by the consultee in any of their comments.
Additional APPENDIX 2 references (not otherwise in APPENDIX 1 references, above) Comments 20, 21, 40, 51, 64, 75,	Barolat G, Oakley JC, Law JD, North RB, Ketcik B, Sharan A (2001) Epidural spinal cord stimulation with a multiple electrode paddle lead is effective in treating intractable low back pain. Neuromodulation 4:59–66	Retrieved, but this study does not seem to have been cited by the consultee in any of their comments.

Themed Comment number(s)	Study reference (as provided by the consultee)	Reason for exclusion against the original literature search scope
143, 144, 156, 165, 166, 174		
Additional APPENDIX 3 references (not otherwise in APPENDIX 1 or APPENDIX 2 references, above Comments 4, 24, 34, 35	Maria Elena Flacco, Lamberto Manzol, Stefania Boccia, Lorenzo Capasso, Katina Aleksovska, Annalisa Rosso, Giacomo Scaioli, Corrado De Vito, Roberta Siliquini, Paolo Villari, John P.A. Ioannidis; Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor - Journal of Clinical Epidemiology 68 (2015) 811e820	Retrieved – not Senza.
Additional APPENDIX 3 references (not otherwise in APPENDIX 1 or APPENDIX 2 references, above Comments 4, 24, 35	Russo M., Cousins M.J., Brooker C., Taylor N., Boesel T., Sullivan R., Poree L., Shariati N.H., Hanson E., Parker J. 2017. Effective Relief of Pain and Associated Symptoms With Closed-Loop Spinal Cord Stimulation System: Preliminary Results of the Avalon Study. Neuromodulation 2017; E-pub ahead of print. DOI:10.1111/ner.12684	Retrieved - wrong system (Evoke; Saluda Medical, Sydney, Australia)
Comments 1, 2, 3, 15 and 176	Thomson ST, M..Love-Jones, S. Patel,N. Jianwen W,,Que D, Moffitt, M. 29 May - 017. PATIENT RESPONSES TO PARESTHESIA-BASED SPINAL CORD STIMULATION AND KILOHERTZ FREQUENCY SPINAL CORD STIMULATION: in International Neuromodulation Societyâ€™s 13th World Congress Neuromodulation: Technology Changing Live	Conference abstract of the PROCO study, now superseded by publication in Thomson *et al.* (2017).
Comment 5	Chella Narendran RG, A. Eldabe,S. West, Garner,F & King,R. HF10TM spinal cord stimulation: Middlesbrough experience (181). Neuromodulation. 2015;18:e13â€“e106.	Was abstract 28 in the conference abstracts provided by Nevro (Narendran *et al*.) Conference abstracts were not reviewed in AR.
Comment 8 (Table 3)	David Abejón. Back Pain Coverage with SCS: What Techniques for Which Patient. NANS 2014	Abstracts / copies provided by the consultee 08/01/2018. Conference abstracts were not reviewed in AR.
Comment 8 (Table 3)	A Gulve, K Koneti, S Eldabe, F Garner, S West, R Chadwick, R King. 10kHz High Frequency Spinal Cord Stimulation: Middlesbrough Experience. NANS 2013.	Abstracts / copies provided by the consultee 08/01/2018. Conference abstracts were not reviewed in AR. NB - this sounds to be same study title as record 28 (Narendran et. Al 2015) in the HF10 Therapy Clinical Evidence Conference Abstracts FINAL provided by Nevro for NICE/EAC info. Conference abstracts were not included, as described in the AR.
Comment 8 (Table 3)	Frank Thomas, MB ChB FANZCA FFPMANZCA, Symon McCallum, MB ChB, FANZCA, FFPMANZCA. High-Frequency Spinal Cord Stimulation (HF10 SCS) for the treatment of chronic pain patients - A real practice experience. NANS 2013.	Abstracts / copies provided by the consultee 08/01/2018. Conference abstracts were not reviewed in AR. In addition, n<10 patients.

Themed Comment number(s)	Study reference (as provided by the consultee)	Reason for exclusion against the original literature search scope
Comment 8 (Table 3)	Russo *et al.* (2013- INS) - We are currently waiting to receive the full reference of this study. We will be providing the information in due course. Apologies for the delay.	Abstract / copy not provided by the consultee, however they did provide NICE with the Russo *et al.* 2016 study instead (presumably full paper arising from these abstracts), which was already addressed in the company submission and AR.
Comment 8 (Table 3)	Brouns *et al.* (2016-WIP) - We are currently waiting to receive the full reference of this study. We will be providing the information in due course. Apologies for the delay.	Abstracts / copies provided by the consultee 08/01/2018. Conference abstracts were not reviewed in AR.
Comment 10/11	HIGH FREQUENCY SPINAL CORD STIMULATION (HF-SCS) AT 10 KHZ RESULTS IN SUSTAINED PAIN RELIEF AND IMPROVED FUNCTIONAL OUTCOMES S. Tripathi[1], M. Kaushal[1], N. Park[1], V. Munukutla[1], H. Monaghan[1] [1]Royal Preston Hospital, Pain and Neurosurgery Departments, Preston, United Kingdom	n=5 and poster only. EFIC Copenhagen 2017. Retrieved from: http://web.kenes.com/KLead/EFIC2017Abstract/data/HtmlApp/main.html#23.
Comment 16	Kinfe, Mohammed *et al.* (Neuromodulation 2016 and 2017)	Was record 13 excluded at second Senza sift (n=6 in HF10 arm with BurstDR comparator out of scope).
Comment 22	"Other published and presented data from Russo, Kinfe, Muhammed, Thomson and Slotty also are non-corroborative of the SENZA RCT data. "	Inadequate citations to be sure, but presume first 4 are the studies EAC is already aware of. There is only one 'Slotty' in the Senza publications sift and this is as a co-author to Schu (Record 155) – was excluded at first sift as wrong device (burst SCS).
Comment 34	Linde K, *et al.* The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. Pain. 2007 Apr;128(3):264-71	Abstract reviewed at https://www.ncbi.nlm.nih.gov/pubmed/?term=17257756 Wrong intervention / population (acupuncture / different chronic pain).
Comment 34	Cormier S, *et al.* Expectations predict chronic pain treatment outcomes. Pain. 2016 Feb;157(2):329-38	Abstract reviewed at https://www.ncbi.nlm.nih.gov/pubmed/?term=26447703 Wrong population (chronic pain - otherwise not specified).
Comment 34	Hrobjartsson A, *et al.* Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome	Abstract reviewed at https://www.ncbi.nlm.nih.gov/pubmed/?term=2237185

Themed Comment number(s)	Study reference (as provided by the consultee)	Reason for exclusion against the original literature search scope
	assessors. BMJ. 2012 Feb 27;344	9 Excluded - not Senza.
Comment 34	Hrobjartsson A, *et al.* Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. CMAJ. 2013 Mar 05;185(4).	Abstract reviewed at https://www.ncbi.nlm.nih.gov/pubmed/?term=23359047 Excluded - not Senza.
Comment 34	Vase L *et al.* Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: A meta-analysis of the individual data from nine industrially sponsored trials. Pain. 2015 May 4;156(9)	Abstract reviewed at https://www.ncbi.nlm.nih.gov/pubmed/?term=25955965 Excluded - not Senza.
Comment 54	Forster M, *et al.* Axial low back pain: one painful area--many perceptions and mechanisms. PLoS One. 2013;8(7):e68273. PubMed PMID: 23844179. PMCID: 3699535. Epub 2013/07/12. eng	Abstract reviewed at https://www.ncbi.nlm.nih.gov/pubmed/?term=23844179 Excluded - not Senza.
Comment 54	Kemler MA, *et al.* Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. The New England Journal of Medicine. 2001 Aug;343(9):618-24	Abstract reviewed at https://www.ncbi.nlm.nih.gov/pubmed/?term=10965008 Wrong population (CRPS) & study date precedes Senza.
Comment 54	de Vos CC, *et al.* Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial. Pain. 2014 Nov;155(11):2426-31	Was record 137 excluded at Senza first sift (wrong population).
Comment 54	Slangen R, Pluijms WA, Faber CG, Dirksen CD, Kessels AG, van Kleef M. Sustained effect of spinal cord stimulation on pain and quality of life in painful diabetic peripheral neuropathy. Br J Anaesth. 2013 Dec;111(6):1030-1	Reviewed at https://academic.oup.com/bja/article/111/6/1030/292743 Wrong population (diabetic peripheral neuropathy) and intervention (Medtronic).
Comment 54	van Beek M, *et al.* Sustained Treatment Effect of Spinal Cord Stimulation in Painful Diabetic Peripheral Neuropathy: 24-Month Follow-up of a Prospective Two-Center Randomized Controlled Trial. Diabetes Care. 2015 Sep;38(9):e132-4	Reviewed at http://care.diabetesjournals.org/content/38/9/e132.long As Slangen *et al.* above, 24 month FU in wrong population (diabetic peripheral neuropathy) and intervention (Medtronic).
Comment 54	Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M.	Reviewed at

Themed Comment number(s)	Study reference (as provided by the consultee)	Reason for exclusion against the original literature search scope
	Spinal cord stimulation for chronic reflex sympathetic dystrophy--five-year follow-up. N Engl J Med. 2006 Jun 1;354(22):2394-6	http://www.nejm.org/doi/full/10.1056/NEJMc055504 As Kemler *et al.* above, 5 year follow up in wrong population (CRPS) and original study date precedes Senza.
Comment 73	De Carolis et al 2017 (Pain Physician 2017; 20:331-341)	Was record 4 excluded at second Senza sift (Wrong outcomes (Technical / therapeutic prescription levels)).
Comment 73	INS2017_McMahon10kHzInVivo_Poster_Ver0519[1]	Provided to NICE by the consultee. Animal studies excluded.
Comment 105	Deer, T., Slavin, K. V., Amirdelfan, K., North, R. B., Burton, A. W., Yearwood, T. L., *et al.* (2017). Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation : Journal of the International Neuromodulation Society, 46, 489. http://doi.org/10.1111/ner.12698	Abstract reviewed at: https://www.ncbi.nlm.nih.gov/pubmed/?term=28961366 Excluded - wrong device (BURST).
Comment 105	Wille, F., Breel, J. S., Bakker, E. W. P., & Hollmann, M. W. (2016). Altering Conventional to High Density Spinal Cord Stimulation: An Energy Dose-Response Relationship in Neuropathic Pain Therapy. Neuromodulation: Technology at the Neural Interface, 20(1), 71 to 80. http://doi.org/10.1111/ner.12529	Was record 20 excluded at first Senza sift (wrong population - failed conventional SCS and mixed CRPS and polyneuropathy).
Comments 107, 145 and 146	Thomson S., Kruglov D., Duarte R. A Spinal Cord Stimulation Service Review from a single centre using a single manufacturer over a 7.5 year follow up period. Neuromodulation 2017; 20: 589 to 599	Retrieved and excluded - wrong device (Precision or Precision Spectra, Boston Scientific, Valencia, CA, USA) However, it is noted for the 'DB1' cohort that this study provides evidence for the battery life of this comparator device at the 7.5 year FU period: "Those patients from DB1 are an older cohort, but there were no signs of increased charging frequency that might have suggested deterioration in the battery to hold a charge."

2.1.2 Studies out of scope but considered of interest to the NICE guidance

Of the studies considered out of scope of the Senza HF10 therapy assessment by the EAC, two recent and emerging studies were of particular interest to the guidance, although they did not include Senza HF10 therapy as the intervention. These were the study by Thomson *et al.* (2017) [8] and Al-Kaisy *et al.* (2018) [9].

2.1.2.1 Thomson *et al.* (2017)

The *Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial* was authored by Thomson *et al.* (2017) [8]. This study was not identified by the EAC during production of the AR because it was accepted for publication in November 2017. It has been excluded by the EAC because the intervention and comparator used was not Senza HF10 therapy, but the Boston Scientific PRECISION Spinal Cord Stimulator System with MultiWave Technology (see NCT02549183). However, in this section the EAC has provided a brief analysis of the trial, for three reasons. Firstly, the EAC considers that the study provides interesting background information with regard to the relationship between SCS device frequency and efficacy, similar to that of the Perruchoud trial [10], briefly discussed in the AR [1]. Secondly, this study was widely cited by stakeholders during the consultation process, including by NHS professionals, as being relevant to the guidance. And thirdly, the trial was set in three hospitals in England (Basildon and Thurrock University Hospitals, Southmead Hospital, Bristol, and James Cook University Hospital, Middlesbrough) which makes the study, in terms of setting, generalisable to the UK NHS.

The PROCO study was a double blind cross-over RCT that enrolled 34 patients with persistent or recurrent back pain with or without leg pain to undergo implantation with the SCS device, initially set at 10 kHz. Patients who successfully underwent the SCS trial (n = 33), with ≤ 50% reduction in pain as measured by the numeric rating scale (NRS) underwent permanent implantation. Following identification of the 10 kHz “sweet-spot” at around 8 weeks, responders (n = 20) underwent randomisation in the order they received SCS at the frequencies of 1 kHz, 4 kHz, 7 kHz, and 10 kHz, with individually titrated pulse width and amplitude to optimise pain relief. This phase of the trial lasted for 8 to 16 weeks, after which the patients chose their preferred frequency and were maintained on this for a further 10 to 12 weeks.

The authors reported that all frequencies resulted in a significant decrease in pain compared with baseline ($p \leq 0.02$). The degree of pain relief at each frequency was similar. However, mean charge per second differed across frequencies, with 1 kHz SCS requiring 60–70% less charge than higher frequencies ($p \leq 0.0002$). There was no significant difference in patient preference for any particular frequency, with about half of those who expressed a preference (n = 7/15) opting for the last frequency they experienced. The authors concluded that there was equivalent pain relief gained from all the frequencies used between 1 kHz and 10 kHz, but that 1 kHz had the advantage of requiring less charge.

Strengths of this study include that it was double blinded so that patients and investigators were unaware of the order of allocation of the frequency in the randomisation stage. This was because all frequencies were above the perception of paraesthesia. However, weaknesses of the study include that it was small, had a high attrition rate, and did not include a sham arm with which to interpret non-specific pain relief effects. Additionally, it should be reiterated that this study did not use Senza HF10 therapy or its specific waveforms, so results should not be extrapolated to this technology.

2.1.2.2 Al Kaisy *et al.* (2018)

The study by Al-Kaisy *et al.* was undergoing peer review for the journal *Neuromodulation* during the public consultation on the guidance, and was shared with NICE and the EAC as AiC material. The full paper of this study, also known as the SCS Frequency Study has since been published [9]. The protocol for the trial had been reported in clinicaltrials.gov (NCT01750229) and was not included in the AR, as it did not feature Senza HF10.

In the SCS Frequency study, patients were enrolled into a cross-over trial where they received SCS from a Medtronic device (RestoreSensor™). All patients had failed back surgery syndrome (FBSS) diagnosed at a mean 5.1 years (range 0.5 to 19.5 years) previously, and back pain, with a mean visual analogue scale (VAS) measurement of 7.75 cm (1.13 SD), was predominant over leg pain (mean VAS 3.06 cm, 2.55 SD). Thirty nine patients were enrolled to have a device trial, of which the device was successfully implanted in 33, with 30 patients randomised. However, following randomisation (to determine order of SCS sequence), 6 patients were excluded, with 24 patients completing the trial and providing the outcome data. Thus there was a high rate of patient attrition.

All patients received SCS at frequencies of 1200 Hz, 3030 Hz, 5882 Hz, and sham for 3 week periods. Investigators and patients were blinded to the allocation, since these are considered sub-perception frequencies, with only the programmer (who took no further part in the trial) aware of the frequency. The sham mode of the device was designed to deplete the battery without either delivering any electrical charge to the epidural leads, or cause noticeable heating, thus masking was retained. The frequency and pulse width were unchangeable for each period, with amplitude variable. Following the cross-over phase of the study, patients could elect to continue use of the device for a further 12 months at their preferred frequency (open label).

The primary outcome of the trial was pain relief, as measured by VAS. The authors reported the absolute VAS for back pain after each period was 4.83 cm for sham, 4.51 cm for 1200 Hz, 4.57 cm for 3030 Hz, and 3.22 cm for 5882 Hz. All the frequencies, including sham, were significantly reduced compared with the 7.75 cm baseline. However, the highest frequency (5882 Hz) provided significantly greater pain relief than all the other frequencies, including sham (mean difference 1.61 cm, $p = 0.003$). There was no significant difference between any of the other frequencies compared with each other. The mean average leg pain scores were 3.06 cm, 2.51 cm, 2.37 cm, 2.20 cm, and 1.81 cm, for baseline, sham, 1200 Hz, 3030 Hz, and 5882 Hz, respectively. There was no significant difference between any of these values and baseline. During the 12-month open label phase, 29% of patients

expressed a preference for 5882 Hz stimulation, 25% of patients reverted to traditional stimulation (low frequency SCS), 21% chose 1200 Hz, 12.5% chose the 3030 Hz setting, while 12.5% requested sham stimulation.

The EAC considers that the SCS frequency study reported two key results. Firstly, the study showed that the higher frequency use, at 5882 Hz, was associated with significantly improved back pain relief compared with all the lower frequencies, and sham. This result is contrary to what was reported by the PROCO trial, where 1 kHz frequencies were as effective as higher frequencies [8]. However, the study also reported that there was a highly significant placebo effect, which in fact accounted for most of the improvement observed in back pain (absolute reduction of 2.92 cm associated with sham compared with baseline). This result is consistent with results from the trial by Perruchoud *et al.* (2012) [10], briefly described in the AR [1]. As with the Perruchoud and Thomson studies, the SCS Frequency study should be considered in the context that it did not use Senza HF10 therapy or its specific waveforms, so results should not be extrapolated to this technology. However, these studies confirm that it would be technically possible to conduct a blinded sham study with Senza HF10 and retain masking. A previous sham study on Senza HF10 was abandoned before completion [11]. The company had claimed the reason for this was because of patient unmasking due to technical reasons [12].

Section 3: Study by Van Buyten *et al.* (2017)

3.1 DESCRIPTION OF STUDY

The study by Van Buyten *et al.* (2017) [4] was a retrospective "chart review" performed in four European centres in three countries (Belgium, the Netherlands, and Germany) that have performed SCS using traditional and high frequency technologies. Patients were selected for review if they had at least 2 years follow up data available. Patients had received SCS for a range of indications, with the most common being prior spinal surgery syndrome (73%) resulting in FBSS or failed neck surgery syndrome (FNSS). The predominant pain location was back and legs (63%). Patients with other conditions, such as complex regional pain syndrome (CRPS) or pain of ischaemic origin, were also included.

The principal aim of the study was to determine if there are any differences in rate of explant for the different types of SCS systems. These systems were categorised as conventional (low frequency) non-rechargeable SCS, conventional rechargeable SCS, and high frequency SCS (Senza HF10 therapy). Both anticipated explantation (replacement due to expired battery life) and unanticipated explantation (removal of device due to complication or failure of efficacy) were analysed. As well as potentially identifying differences between device types, the investigators were able to use the chart reviews to assess the associations between explantation rate and patient characteristics. Data were collected from implants performed between January 2010 to December 2013 (n = 955).

3.2 STRENGTHS AND WEAKNESSES

The study by Van Buyten had several strengths. Firstly, the methodology employed allowed for inclusion of a large number of subjects which might not have been feasible for an RCT. The sample size was sufficiently large to allow for appropriate time to event analysis and subgroup analysis so SCS technologies could be compared. In addition, as routine data were used, it should be generalisable to real world practice. To the EAC's knowledge, this study represented the most comprehensive review of this important outcome, device explantation, currently publically available.

Retrospective studies of this nature also have inherent weaknesses which means outcomes should be treated with caution [13]. As the data are not prospectively collected, there is a necessary reliance on recordkeeping by a third party which may not be accurate or complete. Additionally, the investigator does not have control over specific outcomes and variables measured. Retrospective studies are particularly subject to selection bias and tend to include a less well-defined target population than typical with a prospective study. This is true in the case of this study, which thus has limited generalisability. There was a relatively high loss to follow up in the Van Buyten study, with 75 patients having missing data at later follow up times, and there was incomplete reporting of outcomes (possible reporting bias). The study was funded by St Jude Medical who manufactured a range of conventional and novel SCS technologies.

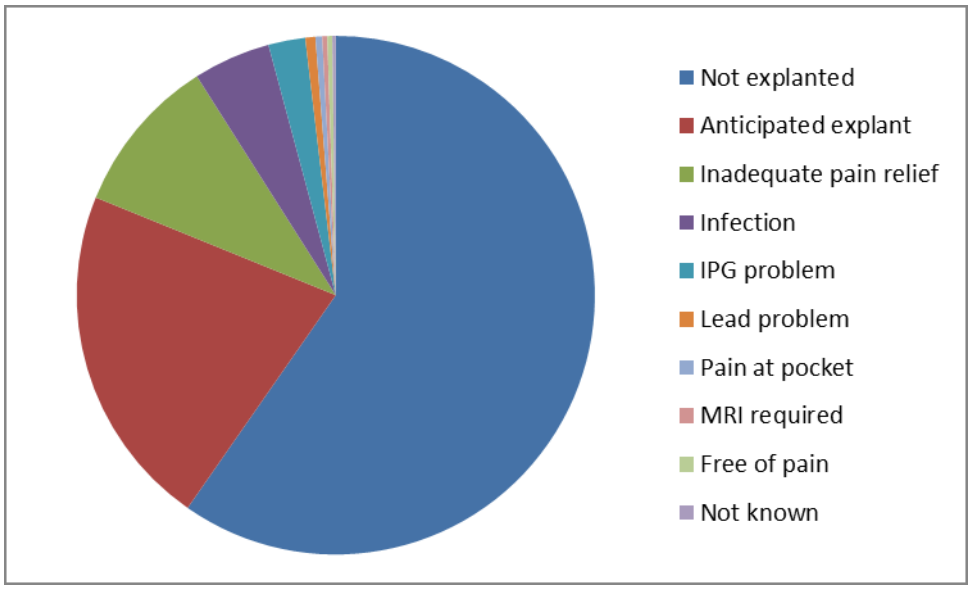
3.3 RESULTS

The Van Buyten study reported data on 955 SCS implants in 822 unique patients. The median age of patients was 53 years, with 58% being female. The most common implant was conventional non-rechargeable (48%), followed by conventional rechargeable (34%) and Senza HF10 (16%), with 1% being less commonly used devices or unknown. There was a median of 7 follow up appointments per patient (range 3 to 12), a median follow up of 2.24 years (range not reported), and the total duration of follow up duration was 2259 person years (PY).

Overall, there were 180 implants removed that fitted the "unanticipated" category, which represented a crude rate of 19%. Ninety four unanticipated explantations (10%) were due to inadequate pain relief. Using time to event analysis, the explantation rate was 8.0% (95% CI 6.9 to 9.2%) per PY overall and 4.2% (95% CI 3.4 to 5.1%) per PY for inadequate pain relief. Both conventional rechargeable SCS and Senza HF10 had significantly higher explantation rates due to inadequate pain relief than conventional non-rechargeable SCS, with relative hazard ratios (HR) of 1.98 ($p = 0.005$) and 1.79 ($p = 0.035$) respectively, using univariate analysis. When multivariable regression analysis was performed, only conventional rechargeable SCS was significantly more likely to be explanted compared with conventional non-rechargeable SCS (HR 1.95, $p = 0.011$). After inadequate pain relief, the biggest reason for removal was infection, with a crude rate of 5% removal (which was 26% of all unanticipated explants), followed by problems with the implanted pulse generator (IPG) with a rate of 2% removal, and lead problems, pain at pocket, freedom from pain (without the need for SCS) and no specific reason identified (all < 1%). Removal so Magnetic Resonance Imaging (MRI) could be performed was also reported as < 1% (3 patients, see Section 6.2). The EAC has considered that the reason for unanticipated explantation other than inadequate pain relief was likely to be proportionally similar for different device technologies (see below). The reasons for device explantation are illustrated in Figure 1.

For comparison, data reported from the SENZA-RCT (AiC) study were limited in detail and had small sample sizes. However, the unanticipated explantation rate due to poor efficacy was reported as [redacted]% for Senza HF10 and [redacted]% for conventional low frequency SCS. These figures were not used in the economic analysis, rather the rates for explantation for any reason were used (see Section 7.2.2).

Figure 1. *Pie chart illustrating explantation rates, and reasons for explantation, after up to 5 years follow up (median 2.24 years) all technology types.*



The Van Buyten study reported the number of unanticipated explants performed because of inadequate pain relief in some detail. The main reason for SCS withdrawal has previously been attributed to the device failing to provide adequate pain relief [14]. However, the study did not report the unanticipated explantation rate by individual device type for *any reason*, which is also highly relevant to the economic model (see Section 7.2.2). In the absence of these data, the EAC has estimated the relative proportions of unanticipated explantation for any reason by extrapolating data from the explantation rate due to inadequate pain relief, assuming constant proportionality. This approach is not entirely satisfactory, because it does not account for any important technical differences that may have been unreported; however it is currently the best estimate available to the EAC for overall explantation rate. Additionally, the rate from three years onwards is an average rate over 5 years follow up calculated using time to event analysis, which may have been skewed due to higher explantation rates at the earlier time points. Ideally, longer term studies are required. The explantation rates reported by Van Buyten are reported in Table 4.

One hundred and seventy three implants (18.1%) were recorded separately as being due to battery depletion and were not counted as unanticipated events. The authors did not report what proportions of these were non-rechargeable or rechargeable, although it would be assumed most were of the former type. This equates to a rate of 7.7% per PY. The large majority of these implants (97%) were replaced. Additional, 38 implants (4.0%) were removed so they could be replaced with devices with additional features, including burst, high frequency, or high-density waveforms, MRI conditional systems, or additional leads. There were 13 deaths during the study period.

3.4 CONTEXT WITH SENZA GUIDANCE

The study by Van Buyten *et al.* (2017) has provided useful, published data on both the anticipated explantation rate, which was principally due to battery depletion, and unanticipated explantation rate, which was principally due to loss of efficacy in achieving

pain relief. The study was a retrospective analysis of routinely collected data which has inherent strengths and limitations (Section 2.2.2). A particular weakness of the study was that it did not fully report the breakdown of explantation for reasons other than inadequate pain relief between device technologies. However, the study did provide useful data within the context of the guidance development:

- The overall unanticipated explantation rate, at 8.0% per PY, was higher than stated for the Senza RCT study (years 1 and 2, data redacted) [15, 16] or from the Health Technology Assessment (HTA) that informed NICE TA159 (3 years onwards) [17].
- Using univariate analysis, the explantation rate for inadequate pain relief was significantly higher for rechargeable devices compared with non-rechargeable, regardless of frequency (conventional or HF). This difference was still observed for conventional rechargeable SCS when multivariable regression analysis was employed.
- Possible explanations for the differences seen in unanticipated explantation between rechargeable and non-rechargeable devices include compliance issues (associated with the burden of recharging), as well as psychological reasons associated habituation. However, as this was a retrospective review this is largely speculative [4].
- Despite the relatively short time frame of the study (median follow up 2.24 years), battery replacement was required in 18% of implants. Unfortunately information on the composition of battery failure according to technology type was not reported.

Table 4. *Unanticipated explantation rate reported in study by Van Buyten et al. (2017) [4].*

Type of SCS	**Number of implants (PY)**	**Explants for inadequate pain relief***	**Explants for inadequate pain relief per year (95% CI)**	**Unanticipated explants for all causes****	**Unanticipated explants for all causes per year****
Conventional non-rechargeable	462 (1125.2)	32 (6.9%)	2.8% (2.0 to 4.0%)	61 (13.3%)	5.4% (3.2 to 7.2%)
Conventional rechargeable	329 (671.5)	37 (11.2%)	5.5% (4.0 to 7.6%)	71 (21.5%)	10.6% (7.3 to 14.0%)
Senza HF10	155 (439.4)	22 (14.2%)	5.0 (3.3 to 7.6%)	42 (27.2%)	9.6% (5.0 to 14.3%)

Abbreviations: CI – confidence interval; PY – person years; SCS – spinal cord stimulation.

* Numbers do not add up to 94 due to exclusion of 3 implants using different technologies (e.g. Burst).
** Data calculated with assumption that explantation for any reason was proportionately associated with explantation for inadequate pain relief for all three technology types.

Section 4: Study by Al-Kaisy *et al.* (2017)

The recently published paper by Al-Kaisy *et al.* (2017) [5] reported extended follow up data to the original study by the same author (also published in 2017) [6]. The latter paper was included in both the company submission [18] and the AR. This study was a prospective case series set in Guy's hospital, UK. Twenty one patients with predominant chronic, severe back pain who were naïve to surgery were enrolled, and initially followed up for 1 year (n = 20) [6]. Patients have since been followed up at 2 years (n = 18, 1 patient died and 1 explanted due to inadequate pain relief) and 3 years (n = 17, 1 patient lost to follow up) [5].

The EAC had considered that the case series was of relatively high methodological quality and reporting quality, but had limited generalisability to the decision problem because none of the patients had experienced surgery and consequently did not have FBSS [1]. In addition, this cohort was notable in that back pain predominated over leg pain.

The primary outcome of the study was pain measurement in the back and legs using VAS. In the initial publication [6], the authors reported there was a significant reduction in pain of the back at all time points following baseline (1, 3, 6, 9 and 12 months), which were 46.9 mm (2.78 SD) at 6 months and 55.9 mm (1.80 SD) at 12 months. At these time points, 75% and 95% of patients were classified as responders, respectively. There were similar results for leg pain, although pain reduction was not significant at 6 and 9 months. In the follow up study, this improvement in back pain was reported to have been maintained at 24 and 36 months, with a change from 79 mm (12 SD) to 10 mm (12 SD, $p < 0.0001$) at the latter time point [5]. Leg pain was also described as significantly reduced at 36 months, from a baseline of 33 mm (21 SD) to 9 mm (13 SD).

As well as significant improvement in back and leg pain compared with baseline, the updated Al-Kaisy paper reported other continued improvements over this longer time frame:

- Functional improvement, as measured by reduction in the Oswestry disability index (ODI) was significantly reduced from 53 (13 SD) to 20 (13 SD, $p < 0.0001$).
- Opioid medication use was reduced, from 88% of subjects using opioids at baseline to 19% after 36 months.
- All subjects would recommend Senza HF10 therapy for their condition, with 17/20 satisfied or very satisfied.
- Significant improvements in Quality of life (QoL) as measured by Euroqol 5 dimensions (EQ-5D) and short form 36 item (SF-36), measured in 11 patients at baseline, 15, and 36 months.

In conclusion, the updated study by Al-Kaisy *et al.* reported that early improvements (up to 12 months) in pain, disability, and QoL were maintained until 36 months in this highly selected cohort.

Section 5: Study by De Andres *et al.* (2017)

5.1 BACKGROUND

The study by De Andreas *et al.* (2017) was published in November 2017 [19], subsequent to the completion of the AR [1]. However, during the consultation period of the draft guidance, several independent consultees identified the De Andres study was a particularly important and relevant study to MT330.

The purpose of this section is to briefly review the new study, compare its results with those of the SENZA-RCT [20, 21] (regarded as the key study supporting Senza HF10 therapy), discuss potential reasons for any observed differences, and to give the EAC's opinion on how this study might impact on conclusions drawn in the AR.

5.2 DESCRIPTION OF STUDY

The study by De Andreas was a single-blind randomised controlled trial that compared the efficacy of Senza HF10 therapy with conventional low frequency SCS in patients with chronic, intractable pain of the trunk and/or limbs that was refractory to conservative therapy for at least 6 months following the development of FBSS. The EAC presumed these patients were naïve to SCS (although this was not stated). Outcomes were reported at multiple time points up to 12 months. The primary outcome of the study (i.e. the outcome that informed sample size) was pain intensity as measured by the numeric rating scale (NRS). This reports pain on a 1 to 10 scale and is broadly comparable to the VAS [22] used in other studies identified in the AR [1]. Several other outcomes were reported, most of which were largely subjective (i.e. were patient related outcome measures [PROMs]).

The De Andreas study was not published in a trial protocol database such as clinicaltrials.gov, and thus was not identified by the EAC as a planned or on-going study (Section 3.8 of AR [1]). The publication of the De Andreas study is reported in considerably greater depth than is typical for a journal publication (at around 12,000 words). As such, the granularity of information surpasses that of the other studies described in the AR.

5.3 CRITICAL APPRAISAL

The EAC has critically appraised the De Andreas study using the *Cochrane Collaboration's tool for assessing the risk of bias in randomized trials* [23] in Table 5. The EAC considered that for the most part, the study was at similar risk of bias to the SENZA-RCT study [20, 21], with two important caveats. Firstly, whilst it was impossible to blind participants, clinical assessors and investigators were blinded in the study, which should lead to a reduced risk in detection bias (biased measurement of outcomes). However, there may have been practical issues with maintaining blinding, and the subjective nature of the reported outcomes meant that cognitive bias from the patient in their pain assessment would have remained a major source of uncertainty. Secondly, the study was not funded or otherwise sponsored by a group with a financial motive for trial success. This is discussed further in Section 3.5.

Table 5. *Critical appraisal of study by De Andres et al. (2017) [19].*

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	Patients allocated to groups according to "computerized list of randomized numbers". However, further information on process not reported. No significant difference in baseline characteristics of patients reported.	Low risk of selection bias.
	Allocation concealment	No information on the method of allocation was reported.	Unclear risk of selection bias.
Performance bias*	Blinding of participants and personnel*	Patients were not blinded because this was not possible due to paraesthesia. Clinical assessors were unaware of the allocation and described as "disinterested third parties".	High risk of performance bias. Patients were not blinded and would probably have been aware that HF10 therapy was a novel therapy through basic internet research. Assessors were blinded although the risk of unintentional unmasking would have been high.
Detection bias*	Blinding of outcome assessment*	Assessors and investigators were blinded to the allocation, although in practice masking may have been difficult to maintain.	Low risk of detection bias.
Attrition bias	Incomplete outcome data*	Subject flow diagram was supplied with reasons for exclusion or withdrawal reported. However intention to treat analysis was not implemented and it is unclear how patients who underwent withdrawal were accounted for in analysis.	High risk of attrition bias.
Reporting bias	Selective reporting	No study protocol reported so primary outcomes were not pre-specified. Rationale for sample size not fully described (based on difference of NRS pain scale of 1). Adjustments for multiple comparisons not performed.	High risk of reporting bias.
Other bias	Anything else, ideally pre-specified.	Study was performed independently of industry. No apparent vested interests in the direction of results.	Low risk of bias.

*Assessments should be made for each main outcome or class of outcomes.

5.4 RESULTS, WITH COMPARISON TO SENZA RCT

The EAC has compared results from the De Andres study with those published in the SENZA-RCT, where applicable (not all outcomes were reported in both studies). Particular emphasis has been given to the outcome of pain reduction, as this was the primary outcome of both studies.

5.4.1 Pain

The SENZA-RCT reported the proportion of patients achieving 50% or more reduction in leg pain as measured using VAS at 6 months as the primary outcome [20]. The study by De Andres did not report this outcome. However, both studies reported longitudinal pain perception using VAS or NRS data respectively and there were important differences between the results reported by the studies. In the SENZA-RCT, back pain reduced in the HF10 arm from a VAS of 7.4 cm in baseline to around 2.4 cm at 12 months follow up. In the low frequency SCS arm, there was a reduction from 7.8 cm to 4.0 cm at 12 months (Table 3.3 of the AR [1]). The difference in pain was significant in favour of Senza HF10 therapy (absolute difference at 24 months: -1.7 cm [95% CI: -2.6 to -0.8, p<0.001]). There were similar results for leg pain.

In the study by De Andres, overall pain reduced in the HF10 arm from a mean of 7.50 at baseline to 6.06 at 12 months (the De Andres study did not discriminate between back and leg pain). In the low frequency SCS, the change was from 7.69 to 5.86 at 12 months. Whilst these results indicated significant reductions in pain over time compared with baseline, the authors did not directly compare the arms of the trial of statistically, but stated “The significant improvement in pain over 12 months followed the same pattern in both groups (conventional SCS and HF SCS [Senza HF10])”. Thus, in contrast to the SENZA-RCT study, there was no indication of significant reduction in pain between the study arms; that is there was no evidence of difference in performance of Senza HF10 therapy compared conventional low frequency SCS in terms of pain relief. However, the authors did report a direct comparison between technologies using the PainDETECT questionnaire [24], and found no significant difference.

A comparison of longitudinal pain reduction associated with Senza HF10 and conventional low frequency SCS as reported in the SENZA RCT and De Andres trial is reported Table 6. This is represented graphically in Figure 2. This clearly illustrates how patients reported similar perception of pain at baseline, which was significantly reduced 3 months after implantation, after which the effect plateaued. However, pain reduction was greater in the SENZA-RCT for both Senza HF10 and conventional low frequency SCS compared with data from the De Andres study. Additionally, the SENZA-RCT reported significantly greater gains in pain reduction for Senza HF10 compared with conventional low frequency SCS, a phenomenon not observed by De Andres.

Table 6. *Comparison of pain relief associated with Senza HF10 treatment compared with conventional SCS, as reported by RCTs.*

	Study	**Intervention**	**VAS pain (cm) or NRS at various time points following permanent implantation (SD, where reported).**					
			Baseline	**Post-procedure**	**3 months**	**6 months**	**12 months**	**24 months**
Back pain	SENZA-RCT*	Senza HF10	7.4 (1.3)	N/R	2.3†	2.2†	2.4†	2.4 (2.3)
		LF SCS	7.8 (1.2)	N/R	3.6†	3.8†	4.0†	4.5 (2.9)
		Comparison	Absolute difference at 24 months: -1.7 (95% CI: -2.6 to -0.8, p<0.001)					
Leg pain	SENZA-RCT*	Senza HF10	7.1 (1.5)	N/R	2.3†	2.8†	2.6†	2.4 (2.5)
		LF SCS	7.6 (1.4)	N/R	4.2†	4.1†	4.4†	3.9 (2.8)
		Comparison	Absolute difference at 24 months: -1.0 (95% CI: -2.0 to -0.8, p<0.003)					
Overall pain	De Andres RCT**	Senza HF10	7.50 (1.52)	4.48 (2.14)	5.83 (2.61)	5.83 (2.23)	6.06 (2.13)	N/R
		LF SCS	7.69 (1.27)	5.10 (2.09)	5.71 (1.70)	5.78 (1.97)	5.86 (2.46)	N/R
		Comparison	Formal statistical testing not performed between Senza HF10 and LF SCS.					

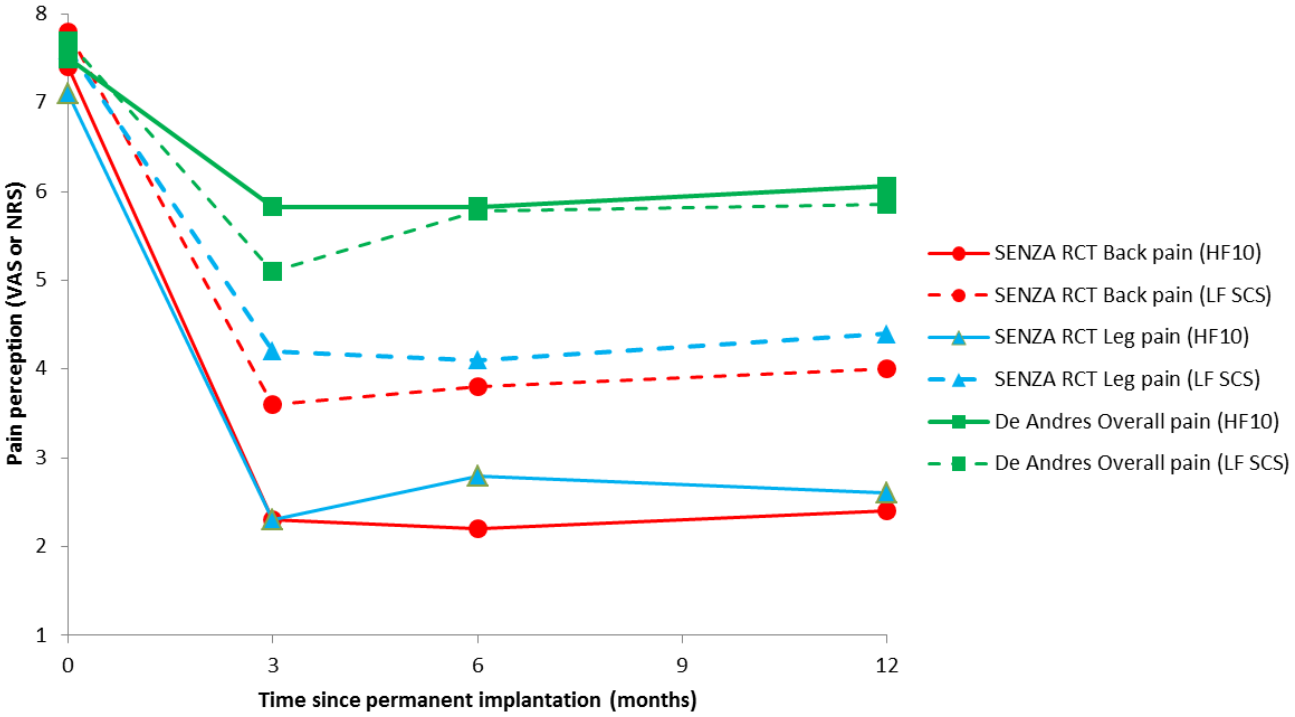
Abbreviations. CI: confidence interval; LF: low frequency; N/R: not reported; NRS: numeric rating score; SD: standard deviation; VAS: visual analogue scale.

* Full longitudinal results of SENZA-RCT VAS pain outcomes presented as graph only.

** Employed NRS system (gives pain rating of 1 to 10, similar to VAS).

† Data estimated directly from graph (Figure 3 of original paper [20]).

Figure 2. *Graphical illustration of pain relief reported in SENZA-RCT [20] and De Andres RCT [7]. Abbreviations: HF10 – Senza HF10 therapy; LF SCS – low frequency SCS.*



5.4.2 Disability

Both studies assessed disability using the ODI scale [25]. The SENZA-RCT reported comparative ODI between Senza HF10 and low frequency SCS arms. At 12 months, 62.9% of HF10 therapy subjects had minimal or moderate disability compared with 45.7% of traditional SCS subjects ($p = 0.03$) [20]. At 24 months, 23.5% of subjects receiving Senza HF10 therapy reported minimal disability compared with 9.9% of low frequency SCS participants [16]. The De Andres study reported significant reduction in ODI from baseline using both technologies, but did not report a significant difference between technologies [7].

5.4.3 Quality of life

The SENZA-RCT did not report QoL outcomes. The study by De Andres measured longitudinal QoL using SF-36 questionnaires. The authors reported no significant differences between Senza HF10 therapy and conventional low frequency SCS in all fields; these were mental health, physical function, role (physical), bodily pain, general health, vitality, social functioning, and role (emotional).

5.4.4 Global impression of change

Both studies reported Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC). The SENZA-RCT study reported that both Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) at 12 and 24 months were superior for Senza HF10 therapy compared with low frequency SCS ($p < 0.01$). There was a statistically significant improvement associated with Senza HF10

therapy compared with low frequency SCS. Using the Global Assessment of Functioning (GAF) at 12 months, 70.8% of subjects receiving Senza HF10 therapy had no symptoms to transient symptoms, compared with 59.3% of traditional low frequency SCS patients. This result trended towards, but did not achieve, significance (p = 0.15).

The authors of the De Andres study reported significant longitudinal improvements in PGIC and CGIC in each arm. However, there were no significant differences observed between technologies with respect to these outcomes.

5.4.5 Complications

Complications and adverse events associated with Senza HF10 therapy have been reported fully in the AR in Section 3.7 [1]. The De Andres study reported only limited information on complications and side effects [7]. These were:

- Two patients (6.5%) receiving low frequency SCS had an unsuccessful trial, compared with three patients receiving Senza HF10 (10.3%, p = 0.446).
- Four patients receiving Senza HF10 (10.3%) had lead migration during the trial phase, compared with none receiving conventional SCS (p < 0.005). The EAC understands that this complication would be transient and fixed during permanent implantation.
- Two patients (6.5%) receiving low frequency SCS experienced lead migration following permanent implantation, compared with one receiving conventional SCS (p = “not significant”).

The EAC considers the low numbers of patients reported for these complication outcomes prevents firm conclusions being drawn.

5.5 DISCUSSION

The recently reported study by De Andres *et al.* (2017) is an important addition to the knowledge base concerning Senza HF10 therapy. In summary, it appears to challenge the results reported not only of the SENZA-RCT study [3, 4], but also observational studies [7-11] which showed a large “before and after” effect compared with baseline [1]. In contrast, the data reported by De Andres only showed a modest longitudinal effect. Conclusions drawn from the SENZA-RCT study stated “long-term superiority of HF10 therapy compared with traditional SCS in treating both back and leg pain” [16], whereas the authors of the De Andres study stated “The evolutionary pattern of the different parameters studied in our patients with FBSS does not differ according to their treatment by spinal stimulation, with conventional or high frequency, in one year follow-up” [7].

The reasons for the difference in reported results are unclear at present. However, it should be noted that results from the De Andres study are by no means definitive and are also subject to considerable uncertainty. This was a small study, with less than 30 participants in each arm. The rationale and basis for determination of the sample size was not transparent to the EAC, and it was unclear if a pre-specified hypothesis was tested. Furthermore, despite wide-ranging reporting of results, back and leg pain were not reported separately, and neither were the proportion of people who responded with 50% pain reduction (the primary outcome used in several RCTs [20, 26, 27] on neuromodulation). Intention to treat analysis

does not appear to have been performed. Although the study was methodologically superior to the SENZA-RCT in terms of blinding (of assessors and investigators), the EAC considers it is improbable that masking could have been fully retained. In any case, the participants were aware of their allocation (because paraesthesia could not be masked) and, as outcomes were subjective and there was no sham control group included, this was probably the greatest limitation methodologically.

Nevertheless, there is a need to understand possible reasons seen between the De Andres study and the SENZA-RCT (and other observational studies). Possible (specific) reasons for differences concerning internal and external validity include the following issues about recruitment and setting, population, study design, and funding. These are summarised in Table 7.

5.5.1 Recruitment and setting

The SENZA-RCT was set in the US, where healthcare is invariably private or insurance based. It is possible that participants were incentivised into recruitment, for instance by being given access to treatment they might not otherwise have afforded. Patients from such a setting may display behaviours not typically presented in the NHS. There may also have been other cultural differences with regards to access and use of healthcare not directly generalisable to the UK. The De Andres study was undertaken within the Spanish healthcare system, which is a tax-based system broadly similar to that of the UK.

5.5.2 Population

The populations of both studies appear to be broadly similar, with those in De Andres being exclusively FBSS, and the majority of the population in the SENZA-RCT having had FBSS (about 77%). However, the population characteristics in the De Andres study are otherwise relatively poorly described, so there is some uncertainty concerning generalisability of the two populations.

5.5.3 Study design

The main difference in the study design was the use of limited blinding in the De Andres study, which may have reduced the potential for detection bias (bias in the measurement and interpretation of outcomes by assessors). Additionally, the authors stated that the use of “standardizing patient programming” reduced differences between programming personnel and their interactions with patients, potentially eliminating another source of bias. The SENZA-RCT did not provide sufficient granularity of information to ascertain if there was a risk of bias through programming. However, there were no apparent differences in the programming parameters described for either technology.

If Senza HF10 therapy was consciously or unconsciously promoted as a “new”, “better”, or otherwise superior technology this could have led to cognitive or expectation bias on behalf of the participants during self-assessment of results at each follow up visit. This could also have been done through exposure of the patient to biased promotional material. Additionally, it is possible that a “nocebo” response could have been elicited in the comparator arm, by the patient having negative connotations associated with the older paraesthesia inducing technology [28]. Treatments of pain conditions, including neuromodulation, have been

observed to be particularly susceptible to the placebo effect [29]. This is supported by evidence from RCTs that have shown sham can significantly reduce pain [10] and that most pain reduction observed by SCS may be due to non-specific responses [30] (see Section 2.1.2.2). However, the EAC would note that deliberate attempts to influence the trial to propagate a placebo response would be considered as a breach of good clinical practice (GCP). There was no indication to the EAC that this occurred.

The EAC had considered in the AR [1] that such bias would be unlikely to fully account for the differential effect of Senza as reported because the effect was substantial and sustained over 2 years; this effect was also observed with the 2-year ACCESS-EU study [31, 32], and more recently a similar effect has been observed by the Al-Kaisy study unpublished subsequent to the AR [30]. However, results from the De Andres study appear to contradict this. A major limitation of both studies was the absence of a sham arm with which non-specific (placebo) effects of SCS treatment could be determined. The EAC considers the information value of sham research would be considerable, especially considering the mechanism of action of HF10 SCS is poorly understood.

5.5.4 Funding

The SENZA-RCT was fully funded by the manufacturer of the device, Nevro corporation. This was in contrast to the study by De Andres, which was “funded by department resources”. Although this is a general issue, it is widely accepted that industry-sponsored studies, where principal investigators have financial ties to the technology, are associated with more positive results than independent studies [33]. This may be due to detectable sources of bias in study design, but may also be due to publication bias which inherently cannot be detected using standard risk assessment tools [34].

Table 7. *Summary sources of potential bias identified in the SENZA-RCT and De Andres study.*

Issue	SENZA-RCT	De Andres RCT	Likely influence of potentially bias
Recruitment and setting	Commercially funded RCT in a US healthcare setting (private).	Independent RCT in a Spanish healthcare setting (public).	Amplify positive results reported in SENZA-RCT.
Population	Well described, most with FBSS.	Poorly described, all with FBSS.	Unclear, although greater certainty that the SENZA-RCT reflects Scope population.
Study design	Open label, no attempt at blinding.	Assessor blinded. Use of "standardised patient programming".	Potential to bias results in favour of Senza HF10. Reduced risk of this in De Andres study.
Funding	Nevro Corporation.	Independent.	SENZA-RCT has unquantifiable risk of bias in favour of Senza HF10.

5.6 IMPACT OF STUDY ON EAC REPORT CONCLUSION

The EAC concluded in the AR that the large and sustained clinical effects reported by the SENZA-RCT, and supported by single-armed observational studies, "provided good comparative evidence for the efficacy and safety of Senza HF10, [although] there remain some gaps in the evidence base" [1]. The EAC assumed GCP had been practised when drawing this conclusion, which it considered should limit the impact of the potential sources of bias identified.

The study by De Andres *et al.* (2017) has been published subsequent to the AR. This was a small RCT that compared Senza HF10 therapy with low frequency SCS in a comparable population to the SENZA-RCT study. The study was methodologically superior in that it blinded the assessors and investigators. In addition, the study was funded independently of industry. Results from the De Andres study indicated the benefit of SCS in general in terms of pain and reducing associated disability was less than had previously been reported. This report of diminished benefit may have wider implications for TA159 [35]. However, the study also reported no significant difference between Senza HF10 and conventional low frequency SCS in pain and disability domains. Thus, whereas previously the EAC had considered there was unequivocal published evidence in support of the superiority of Senza HF10 therapy over low frequency SCS, there is now conflicting evidence on this. This reduces the certainty of the clinical conclusions in the AR.

Although the De Andres study does not support superiority of Senza HF10 compared with conventional low frequency SCS, nor does it suggest clinical inferiority. As clinical superiority

(in terms of pain reduction or related outcomes) was not an input into the *de novo* cost consequence model reported by the company in the submission, the economic outcomes are unchanged (see Section 7.1). Finally, other patient benefits associated with Senza HF10 therapy, such as eliminating paraesthesia, and therefore allowing patients to drive, are unchanged.

Section 6: Characteristics of the technology

6.1 BATTERY CHARGING AND BATTERY LIFE

Some concerns were expressed by stakeholders at consultation that the claimed Senza IPG battery life of 10 years may not be realised in practise. A further concern was that a routine daily recharging burden may deplete the battery performance to an extent that a greater charging frequency (more than once per day) would be required, inconveniencing the patient, or that early explanation and replacement, with cost implications, would occur.

The company provided the Senza SCS Physician Implant Manual (10186-Rev.-J-Physician-Manual-(International)) as part of their original evidence submission to NICE. This states:
"The rechargeable implant battery should provide at least 10 years of service on typical high frequency stimulation settings.[1] If lower power stimulation parameters are used to deliver therapy, the battery should provide service for a longer period of time. At typical low frequency stimulation settings, the implant battery should provide 25 years of service or more. As is to be expected with all rechargeable batteries, over time, patients may experience shorter intervals between recharging. The implant will need replacement when stimulation can no longer be maintained with routine charging.
[1]Nevro Report RD0032 Rev 1"

As part of this advisory work in response to the public consultation, the EAC requested the above "Nevro Report RD0032 Rev 1" document from the company (see updated EAC correspondence log [12]). The latest version of this IPG battery engineering test report was promptly provided to the EAC by the company, as commercial in confidence (CiC) material [36]. A clinical scientist and senior clinical technologist within the EAC reviewed the engineering test report and identified no concerns with the testing protocol. The results were transparently reported and assumptions were reasonable, with conservative margins applied.

Regarding the frequency of recharging, the EAC noted the following in the FDA Summary of Safety and Effectiveness Data (SSED) [37]:
"Battery Charge/Discharge Cycle Verification (Longevity). For 12-hour therapy days the longevity of the batteries on a single charge shall > 4 days and for 24-hour therapy days and longevity of the batteries on a single charge > 10 days."
The EAC asked the company to confirm that the battery would last longer on a single charge for a 24 hour therapy than a 12 hour therapy [12]. Their response is reproduced below.

"The battery life depends on the programmed parameters and on the lead impedance. When delivering therapy 12 hours a day (On Time 10 ms, Off Time 10 ms) with an amplitude of 2.5 mA, stimulation frequency of 10 kHz, pulse width of 30 µs and a global lead impedance lower than 700 Ω, the longevity of the batteries shall be more than 4 days. When delivering therapy 24 hours a day with an amplitude of 7.0 mA, stimulation frequency of 60 Hz, pulse width of 0.3 ms and a global lead impedance lower than 700 Ω, the longevity of the batteries shall be more than 12 days."

These specifications of 4 and 12 days battery longevity, for a range of patient therapy parameters, exceed the recommended daily recharge frequency for the device. The EAC therefore considers the company claims of 10 and 25 years of battery life, for higher and lower power stimulation settings, respectively, to be supported by the technical evidence provided (CiC) [36].

6.2 MAGENTIC RESONANCE IMAGING (MRI) COMPATIBILITY

Four of the stakeholder consultation comments were concerned with the MRI compatibility of the Senza device. At the time of the original EAC evaluation (July 2017), the device was CE marked as MRI Conditional (with restrictions), for head and extremity imaging only, at 1.5 Tesla (T).

The company provided NICE with new documentation (11095-ENG Rev D Nevro 1.5T and 3T MRI Guidelines for Senza) [38] that confirms the Senza SCS system is now CE marked as Full-Body MRI Conditional labelled (News release 15/11/2017). This extends to full-body MRI at 1.5T and head and extremity MRI at 1.5T and 3T, although noting the following restrictions. “MRI Conditional” is not the same as “MRI Compatible”. There remain a number of components of the Senza system which are either MRI Conditional for head and extremity imaging only (e.g. surgical leads, as opposed to percutaneous leads, which can tolerate full body MRI at 1.5T, under specified conditions), or are MRI Unsafe (the trial stimulator, patient remote, charger, programmer wand, clinician programmer and some lead adaptors).

A number of MRI conditional, compatible and incompatible SCS systems are available through NHS Supply Chain and the EAC understands that the choice of system for implant is made by the medical consultant, according to each individual patient’s prognosis, including any planned regular imaging, post-SCS implant. The EAC therefore considers MRI compatibility to be an equivalent consideration for device selection for both the intervention (HF10 therapy using Senza SCS) and comparator(s) in this evaluation (low frequency SCS systems up to 1200Hz).

Furthermore, Van Buyten *et al.* (2017) [4] is a retrospective chart review study at 4 implanting centres in 3 European countries (2010 to 2013) of 955 implants, with 8720 visits over 2259 years of follow-up. Of all reasons documented for unanticipated explant, only 3/955 (<1%) were because an MRI was required.

Section 7: Economic model and costing

7.1 RELATIONSHIP OF CLINICAL EFFICACY AND COSTS IN THE ECONOMIC MODEL

The EAC has fully critiqued the company's model in the AR [1], and the intention of this manuscript is not to repeat work already undertaken. However, the EAC has considered that one issue, which has been the subject of comment from several consultees, requires further clarification. This relates to the impact of clinical evidence on the outcomes reported by the model.

The company's model was based on the cost-utility analysis originally produced to support TA159 [14] and subsequently developed so rechargeable low frequency SCS could be compared with non-rechargeable SCS [39] and then so Senza HF10 could be compared with these technologies [40]. The *de novo* model submitted by the company was also a cost utility analysis. Cost utility analysis is a specific type of cost effectiveness where the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health is analysed, with the outcome measured in incremental cost effectiveness ratios (ICERs).

However, because MTEP requires that notified technologies are cost-saving and at least equally effective as the comparator, or cost neutral with additional benefits or effectiveness, cost consequence analysis is preferred to inform medical technologies guidance [41]. To address this, upon presentation of results, the company stripped the utility outcomes from their results, meaning that only monetary values (absolute and incremental) were reported to support the submission. This was appropriate and within process.

The conversion of the cost utility model to a *de facto* cost consequence model resulted in some limitations to the model and its ability to discriminate between technologies. Following the short-term decision tree section of the model, patients who had a successful trial were categorised as having optimal or sub-optimal pain relief at 6 months, based on responder data derived from the SENZA-RCT. Once a patient was categorised, they could not switch from optimal to sub-optimal pain relief (or vice versa) for the remaining time in the (Markov) model, with the only other transitions possible being death or explantation. In the cost-utility model, the pain state was important as it was associated with different QoL utilities (being lower in the suboptimal pain clinical state). However, in the cost consequence version of the model, there was no difference in costs attributed to either pain state, as they both received the same amount of conventional medical therapy (the company claimed this was a conservative assumption). The consequence of this was that the degree of pain relief, which was the primary outcome of most the clinical studies, had no impact on the company's economic model.

An additional limitation of the study by De Andres is that it did not report the proportion of patients who were responders, nor did it provide patient level data with which this could be calculated. Consequently, this study could not be used to update the cost-utility study in its current structure. Thus the new clinical evidence identified by consultees should be considered in terms of implications for patient benefits only, separate from cost considerations.

7.2 ADDITIONAL SENSITIVITY ANALYSIS

The company had provided extensive sensitivity analysis of the *de novo* model in their submission [18]. This included univariate analysis (with Tornado analysis to identify cost-sensitive parameters), threshold analysis, scenario analysis, and probabilistic sensitivity analysis. The EAC had confirmed the sensitivity analyses were appropriate and had been applied correctly [1]. This section reports how new evidence that has come to light subsequent to the company submission impacts on the costing estimates of Senza HF10.

7.2.1 Clinical efficacy

Two studies reported new evidence on the clinical effectiveness of Senza HF10 therapy in terms of pain reduction; these were the extended follow up of the case series by Al-Kaisy *et al.* (2017) [5] and the RCT by De Andres *et al.* (2017) [7]. The former study did not report a comparator and was conducted in a non-generalisable population. The latter study did not report on the proportions of patients who elicited a 50% reduction in pain, nor was there the granularity of information to calculate this (although the longitudinal data reported suggest there were very few, if any, responders). Thus neither study reported data that could inform the economic model. In any case, as discussed, data on pain relief would not affect the cost outcomes of the model.

7.2.2 Explantation rate

The explantation rate of Senza HF10 and its comparators are important as they are key drivers of the economic model. In the company's submission [18], the explantation rate for the first two years were reported from data reported as AiC from the SENZA-RCT [20]. Explantation rates in later years were estimated from data taken from the AR that informed TA159 [14], which in turn were from the PROCESS study [27].

The study by Van Buyten *et al.* (2017), discussed in Section 3, has since published relatively current explantation data for Senza HF10, conventional rechargeable SCS, and conventional non-rechargeable SCS [4]. This study, which was conducted in a real-world setting rather than the less generalisable setting of an RCT, reported significantly higher rates of unanticipated explantation rates for both rechargeable technologies than had been reported previously. Whereas the SENZA-RCT reported (AiC) explantation rates for the Senza HF10 and Precision Plus Systems (Boston Scientific) only, the Van Buyten study also provided data on non-rechargeable device explantation rates, which were considerably lower in the 5 years of follow up. An additional weakness of the explantation data reported from the SENZA-RCT was that it reported a low number of events such that the addition of a single event could materially affect results. Explantation data available to the EAC are reported in Table 8. These data have been used to inform the economic analysis.

Table 8. *Estimates of explantation rates for conventional and non-conventional SCS and Senza HF10.*

Technology type	Year	Company estimate (95% CI)* (n = 171)	Van Buyten (explantation to inadequate pain relief)** (n = 955)	Van Buyten (explantation to any reason)**† (n = 955)
Conventional low frequency non-rechargeable	Year 1	[redacted]% ([redacted] to [redacted]%)[1]	3.6%	6.9%
	Year 2	[redacted]% ([redacted] to [redacted]%)[1]	3.9%	7.5%
	Year 3 onwards	3.2 (0 to 15.8%)[2]	2.8%	5.4%
Conventional low frequency rechargeable	Year 1	[redacted]% ([redacted] to [redacted]%)[1]	9.3%	17.8%
	Year 2	[redacted]% ([redacted] to [redacted]%)[1]	4.5%	8.6%
	Year 3 onwards	3.2 (0 to 15.8%)[2]	5.5%	10.6%
Senza HF10	Year 1	[redacted]% ([redacted] to [redacted]%)[1]	7.2%	13.8%
	Year 2	[redacted]% ([redacted] to [redacted]%)[1]	5.6%	10.7%
	Year 3 onwards	3.2 (0 to 15.8%)[2]	5.0%	9.6%

* Company estimate derived from patient level data from the SENZA-RCT (AiC). This was accepted by the EAC and MTAC for the base case analysis.
** Data reported by Van Buyten study (2017) without extrapolation [4]. Data for 1 and 2 years reported directly from annual data. Data for 3 years onwards calculated using time to event analysis (potential for bias).
† Data extrapolated from Van Buyten study, see Section 3.3.
1. Source: SENZA-RCT (unpublished data).
2. Source: Assessment report for TA159 [14].

The data reported in Table 8 have been used to create two scenarios for sensitivity analysis. In the first, data reporting unanticipated explantation due to inadequate pain relief have been taken directly from the study by Van Buyten (for all treatment modalities). In the second scenario, the EAC extrapolated data have been used. The impact of these changes on costs is reported in Table 9.

Table 9. *Sensitivity analysis using explantation data from Van Buyten et al. (2017) [4] (15 year time horizon).*

Data source	Cost Senza HF10 (£)	Cost conventional non-rechargeable SCS (£)	Cost conventional rechargeable SCS (£)	Δ Cost conventional non-rechargeable SCS (£)	Δ Cost conventional rechargeable SCS (£)
Company submission (base case)	87,400	95,156	92,196	**7,756**	**4,796**
Van Buyten (unanticipated explant for inadequate pain relief)	90,071	93,043	92,557	**2,972**	**2,486**
Van Buyten (explanted for any reason)	95,837	95,485	98,128	**-352**	**2,291**

Abbreviations: SCS – spinal cord stimulation.

Green shows that Senza HF10 is cost saving. Red shows that Senza HF10 is cost incurring.

As can be seen, the revised estimates of explantation reduce the cost saving potential for Senza HF10 when unadjusted data from the Van Buyten study are used, but cause Senza HF10 to be cost incurring compared to conventional low frequency SCS technologies when the EAC extrapolated data are used. However, the difference is small, at £351 over a 15 year period, or £23.40 per year. Due to the uncertainties involved, the EAC would consider this to be within the margin of error and consider Senza HF10 to be cost neutral compared conventional non-rechargeable SCS. In addition the following caveats should be considered:

- Data for conventional low frequency SCS reported in the Van Buyten study were from various devices, in contrast to Senza HF10 which is a single technology. It is possible that some individual conventional technologies may perform worse than others.
- The data from Van Buyten were derived from a heterogeneous sample of patients with multiple pain aetiologies. This causes uncertainty as to the generalisability to the narrower group of patients described in the Scope.
- The EAC has extrapolated data from the Van Buyten paper because of incomplete reporting. This may not accurately reflect the real data. In addition, rates for 3 years onwards were estimated from annual rates fusing time to event analysis. This may not reflect the reality of higher explantation rates nearer the implantation date.
- Conventional low frequency SCS was not considered to be an appropriate comparator by some consultees.

7.2.3 Minor complications

The rate of minor complications associated with SCS technology types was not a key driver in the *de novo* model, with sensitivity analysis indicating changes to this value had little effect on the cost outcomes. None of the newly identified studies provided usable data to inform this input.

7.2.4 Battery life

No usable evidence was identified concerning the battery life of Senza HF10 and its comparators. However, some consultees provided anecdotal evidence, or unsourced commercial evidence, that the battery life of non-rechargeable low frequency (base case 4 years) had been underestimated when advances in battery technology were taken into consideration. Threshold sensitivity analysis provided by the company [18] reported that if device life of non-rechargeable SCS was extended to 7.5 years or above, Senza HF10 would cease to be the most cost saving option.

7.2.5 Costs

No new evidence on costs was identified during consultation, therefore no update is required.

Four of the stakeholder consultation comments highlighted the recent CE marking of a new 'Senza II' device (News release 30/11/2017) [42], hence the EAC asked the company for further information on the cost implications of this for the NICE assessment (NYEAC 2018). Their response is reproduced below.

"Senza II is a different product than the Senza SCS system which Nevro notified to NICE for evaluation by MTAC. Senza II received a separate CE mark very recently. The device has advantages for a select number of patients in whom the overall size of the IPG is especially important owing to individual patient characteristics such as low Body Mass Index (BMI) and in whom the first Senza device would not be as suitable. Senza II provides a solution to this very specific need. It is estimated that a small number of patients would be eligible and therefore receive Senza II devices in the UK. Having recently received CE mark for Senza II, there is a very gradual limited market release planned in the UK which will introduce Senza II to physicians during 2018. As such, adoption of the new product is expected to remain very low in comparison with the first device, the Senza SCS System. Consequently the Senza SCS system which NICE are evaluating through this process will remain our principal product globally and will continue to be the focus of the company.

Other manufacturers have recently released smaller devices, for example the Medtronic Intellis device, that are marketed to address specific needs of particular subgroups of pain patients. These niche devices have different costing variables and evidentiary support which were not included in the submission. The approach in this evaluation was to compare Senza with other current, widely available and generally applicable SCS devices from other manufacturers such as the Boston Precision device which was selected as the comparator device in the SENZA-RCT trial.

In the context of this evaluation, Senza SCS system is the device upon which all submitted clinical and cost-effectiveness evidence is based. Indeed Senza II has not been subject to cost effectiveness evaluation so it would be inappropriate to include the new device in an evaluation process at this time. Nevro understands that final recommendations from MTAC will therefore not apply to Senza II but will be limited to Senza SCS system in line with the Scope."

Threshold sensitivity analysis produced by the company reported that Senza HF10 would remain cost saving at a cost of up to £22,368 compared with conventional low frequency non-rechargeable SCS and £20,185 compared with conventional low frequency rechargeable SCS. The EAC has repeated this analysis using the revised explantation data from the Van Buyten study [4] (see Section 7.2.2). Under this scenario, Senza HF10 would remain cost saving compared with:

- Conventional non-rechargeable low frequency SCS at a cost of £16,339 (£309 less than the base case price of £16,648).
- Conventional rechargeable low frequency SCS at a cost of £18,663 (£2015 more than base case).

Thus, using the revised data, there is little or no flexibility for the cost of Senza or a successor device to increase before it becomes cost-incurring.

7.3 CONCLUSION OF IMPACT OF NEW ECONOMIC EVIDENCE ON ASSESSMENT REPORT

The EAC has considered how the new evidence identified through the consultation may impact on the economic analysis undertaken to inform the guidance, and where appropriate has reran the economic model with alternative inputs. Two studies were identified which reported updated [5] or new [7] clinical evidence. In particular, the RCT by De Andres [7] reported clinical results that were at variance with those reported by the SENZA-RCT [20]. However, because MTEP advocates a cost consequence approach, where costs and clinical benefits are considered separately, results from this study did not impact on the costing estimates derived from the model.

The study by Van Buyten *et al.* (2017) was a retrospective chart review that reported real-world explantation data [4]. The explantation rate is a key driver of costs in the economic model. When the EAC performed scenario sensitivity analysis using extrapolated data from this study, it was found that low frequency SCS was approximately cost neutral compared with Senza HF10 therapy. This analysis required several assumptions so is subject to uncertainty.

No data on minor complications or IPG battery life were identified which would affect the outputs of the model. Nevro have developed a new high frequency device called Senza II which may be priced differently. This device should not be considered as interchangeable with the Senza HF10 device which is the subject of this guidance.

Section 8: Discussion overview

The purpose of this document was to review new clinical evidence identified by stakeholders during the consultation process, and assess the impact of this on the clinical and economic conclusions made by the EAC previously in the AR [1]. After sifting through 68 publications, 3 were identified as being within the scope of the decision problem [3].

The study by Al-Kaisy *et al.* (2017) reported extended follow up of a study included in the AR [6]. This was a small case series that reported significant longitudinal benefits associated with Senza HF10, in terms of pain reduction and PROMs, being maintained for at least 3 years post implant. This study was conducted in a highly selected population of patients not typical of those who usually receive SCS for neuropathic back or leg pain, and had no comparator arm. It does not materially impact on previous conclusions.

The study by De Andres *et al.* (2017) was an RCT that compared Senza HF10 with conventional rechargeable low frequency SCS over 1 year. It reported both technologies were associated with only modest improvements in pain reduction and PROMs compared with baseline, in comparison to observations in previous studies. Additionally, the study did not find any important significant differences between the technologies. These results were not consistent with those reported in the SENZA-RCT [20]. Both trials were subject to several potential sources of bias, with the SENZA-RCT study, which was open label, being particularly susceptible to performance and detection bias, which could have accounted for some of the differences reported between studies. The EAC has therefore changed its opinion that there is unequivocal evidence to support the superiority of Senza HF10 over conventional low frequency, and now considers the evidence is equivocal. Evidence from the De Andres study did not impact on the economic evidence.

The study by Van Buyten *et al.* (2017) was a retrospective chart review that reported on the explantation rates for Senza HF10, and conventional rechargeable and non-rechargeable low frequency SCS in a heterogeneous case mix of pain patients [4]. The EAC used data extrapolated from this study to run additional sensitivity analysis on the economic model. The results suggested that, under certain assumptions, Senza HF10 may be approximately cost neutral compared with non-rechargeable low frequency SCS, rather than cost saving.

In addition to the review of new published evidence, the EAC reviewed technical documentation pertaining to the battery used in the Senza HF10 device, and were satisfied this supported the battery should be fit for purpose over the 10 year period stated in the submission. The EAC also considered that issues concerning MRI compatibility were out of scope for the committee's consideration.

In summary, the publication of new RCT evidence on HF10 conflicts with the previously published SENZA-RCT study and there is now therefore considerable uncertainty concerning the relative benefit of Senza HF10 compared with conventional low frequency SCS. It is possible that a substantial proportion of pain reduction observed in SCS is due to non-specific effects, such as the placebo effect. In addition, it is possible that the

explantation rate for Senza HF10, derived from AiC data from the SENZA-RCT, does not reflect real-world explantation data. This diminishes the cost saving potential of the technology. The implications of this new evidence should be considered by MTAC when making its recommendations.

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Advice on Senza HF10 SCS public consultation comments on MTCD2

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Section 1: Introduction

This is the second advisory document from Newcastle and York External Assessment Centre (NY EAC); supplementary to the original Assessment Report of Senza HF10 SCS (November 2017) [1] and the first advisory document from NY EAC, (Jan 2018) [2], post-public consultation on the original Draft NICE Medical Technologies Guidance.

Following the public consultation on the second draft of the NICE Medical Technologies Guidance for Senza HF10 therapy, published within the Medical Technologies Consultation Document (MTCD2) (April 2018), a large number of comments were received in relation to the clinical evidence, and in particular the randomised controlled trial (RCT) by De Andres *et al.* (2017) [3]. This study, published in *Pain Medicine*, was edited by Richard North and Sam Eldabe and initially was very well received in their accompanying editorial [4].

However, following the publication of the De Andres RCT, concerns relating to conduct of the trial were expressed by the neuromodulation community. Some of these concerns were addressed by the editors (North and Eldabe) in the form of a published letter in *Pain Medicine* in April 2018 [5], following dialogue with the principal investigator (PI, Dr Jose De Andres).

The purpose of this second advisory document from Newcastle and York EAC is to provide a summary to the NICE Medical Technologies Advisory Committee (MTAC) of the issues raised in the public consultation comments on MTCD2, including those addressed by the North and Eldabe Letter to the Editor of the Pain Medicine journal (April 2018) [5]. The issues are presented in Table 1, which is a top level summary on how the latest public consultation comments might impact on the relative weighting of the SENZA-RCT and De Andres study in the assessment of this technology. Table 1 links to Notes in Section 4, where the EAC's rationale is discussed in more detail. The themes discussed are:

1. Study design;
2. Regulatory bodies, conduct, Good Clinical Practice (GCP) and registration;
3. Blinding;
4. Population;
5. Intervention;
6. Comparator;
7. Outcomes (also see Appendix One);
8. Trial (for implantation);
9. Funding.

In Section 3, the EAC offers its current interpretation of how the responses presented by consultees might affect overall conclusions in the NICE assessment of this technology. This is done by comparing the two RCTs with each other, but also in the wider context of the evidence base discussed in the Assessment Report (AR) [1]. This section reflects EAC opinion and is therefore open to a degree of subjectivity.

Section 2: Tabulated summary of RCTs

Table 1. Comparison of key themes from public consultation comments in MTCD2.

Domain*	SENZA-RCT [6, 7]	De Andres [3]	EAC comment
Study design[4.1]	Prospective randomized, parallel-arm, non-inferiority study. Multicentre USA.	Prospective randomized, parallel-arm, superiority study. Single centre, Spain.	Although the SENZA-RCT was designed as a non-inferiority trial, superiority results were reported, which was acceptable [8]. There was controversy whether the De Andres study was actually an RCT. The EAC has concluded in all likelihood it was a pragmatic RCT as described.
Regulatory bodies, conduct, GCP and registration[4.2]	FDA regulated (phase III trial, required for PMA). CONSORT methodology [9]. Registered on clinicaltrals.gov. (NCT01609972).	Regulatory oversight unclear. Did not adhere to CONSORT methodology. Protocol was not registered.	The SENZA-RCT trial was registered and complied with FDA regulation and GCP though CONSORT. The De Andres study did not register a protocol and w exhibited poor quality reporting, possibly increasing its susceptibility to reporting bias.
Blinding[4.3]	The study was open label with patients, clinicians, assessors, analysts, and investigators being aware of interventional allocation.	The study blinded clinical assessors who made measurements on pain and disability metrics.	The EAC maintains the De Andres study was a single blind RCT, which should lower detection bias. However, the risk of unmasking would be considerable. Both studies would be at high risk of performance and other biases.
Population[4.4]	Most patients (about 77%) had FBSS and pain diagnoses described (although nature of pain [e.g. neuropathic] was not). Mean pain VAS (back, HF10) – 7.4 cm.	All patients had FBSS but pain diagnosis not described. Neuropathic pain categories from PD-Q scores reported. Mean pain NRS – 7.7	Both studies had deficiencies in the reporting of the baseline characteristics of included patients. The study by De Andres notably did not report the underlying pain pathology, whereas the SENZA-RCT did not report the degree of neuropathy. Analysis of baseline ODI data suggests patients in the SENZA-RCT had greater levels of functional disability.

Domain*	SENZA-RCT [6, 7]	De Andres [3]	EAC comment
Intervention[4.5]	Senza HF10 therapy Programming undertaken by Nevro employee.	Senza HF10 therapy Lead placement described. Programming sessions run by a team including "a representative of the device manufacturer".	The application of the intervention, Senza HF10, was poorly and confusingly described in the De Andres study, and was potentially suboptimal for an unquantified number of the included patients. However, the EAC is satisfied that Senza HF10 therapy had been applied to the patients following permanent implantation. A letter to NICE from Nevro Corp. does not contradict this opinion (see Appendix Two).
Comparator[4.6]	Programming of comparator performed by Boston Scientific.	Programming of technologies performed by a team including representatives of respective companies.	The EAC is satisfied that potential bias in the programming of the comparator devices has been adequately addressed.
Outcomes[4.7]	Primary outcome was proportion of patients responding to SCS (≥50% reduction in pain measured by VAS) Secondary outcomes PROMs, tertiary outcomes QoL.	Primary outcome was ≥50% reduction in pain measured by NRS (intra- and inter-group). Secondary outcomes PROMS and QoL.	Outcomes were more transparent in SENZA-RCT, with primary outcome predefined and clearly reported. Additional QoL and PROM data recently published [10] (see Appendix One). Primary outcome and many secondary outcome data reported superiority of SENZA HF10 (but not generic QoL). The study by De Andres did not adequately report primary outcome (inference is that it was not achieved in either arm). Superiority of SENZA HF10 not reported in any important outcome.
Trial [4.8] (for permanent implantation)	≥40% reduction in baseline pain required for permanent implantation. Achieved in 90/97 (92.8%) in HF10 arm and 81/92 (88.0%) in LF SCS arm	≥50% reduction in baseline pain required for permanent implantation. Achieved in 26/29 (90.0%) in HF10 arm and 29/31 (93.5%) in LF SCS arm	Response rates (to the trial phase) and follow up responses were poorly reported in the De Andres study. Upon careful reading of the text, the EAC has judged it is probable that patients were appropriately selected for permanent implantation (i.e. had experienced 50% pain reduction during the trial).
Funding[4.9]	Trial was funded by Nevro Corp. The EAC was satisfied that the PI and other	The study was independently funded. The EAC has not identified any personal,	The EAC considers that, whilst it is factually correct that commercially sponsored trials tend to publish optimistic results [11], there was no evidence of overt financial issues with the

Domain*	SENZA-RCT [6, 7]	De Andres [3]	EAC comment
	investigators did not have personal, financial, conflicts of interest in the trial.	financial, conflicts of interest for the PI in any of the device manufacturers.	SENZA-RCT. The EAC did not identify any specific motive for investigator bias in the De Andres study.

Abbreviations: FDA – (US) Food and Drugs Administration; GCP – good clinical practice; HF10 – high frequency (10 kHz); LF SCS – low frequency spinal cord stimulation; NRS – numerical rating scale; ODI – Oswestry Disability Index; PI – principal investigator; PD-Q – pain detection questionnaire; PMA – pre-market approval; PROMs – patient reported outcome measures; QoL – quality of life; RCT – randomised controlled trial; VAS – visual analogue scale.
* There are notes associated for each domain intended to substantiate further the EAC's opinion.

Section 3: EAC discussion and conclusion

3.1 DISCUSSION

Following the first draft of the Senza HF10 guidance, opened to public consultation as the first medical technologies consultation document (MTCD) in November 2017, the EAC produced an Advisory report for MTAC [2] which addressed consultee criticisms of the SENZA-RCT [6, 7], appraised the newly published study by De Andres [3], compared outcomes of these studies, and attempted to identify potential reasons for the discrepancies reported.

Following the second public consultation (MTCD2) in May 2018 and publication of a Letter to the Editor of the *Pain Medicine* journal (North and Eldabe) [5] in April 2018, the De Andres RCT has been subject to extensive criticism from consultees, with some requesting its withdrawal from consideration in the NICE assessment of the Senza HF10 therapy. This second advisory document from the EAC has summarised the themes of the consultation issues and the EAC's position on these. Also in this document is a brief review by the EAC of one emerging publication from the SENZA-RCT (Amirdelfan *et al.* 2018) [10] (Appendix One), which was sent to NICE after the closing date of the second public consultation.

Pain relief results from the De Andres study differed from the SENZA-RCT in two important ways. Firstly, results for both technologies were worse than described in the SENZA-RCT, but also conventional LF SCS was worse than had previously been reported in the PROCESS trial [12] and North trial [13], used to inform NICE TA159 [14]. Secondly, the De Andres RCT did not detect any important differences in pain reduction, or other measures, between the technologies. It is the latter finding that is of central importance to the recommendations of the final NICE guidance (in accordance with the Final scope for the assessment).

Several consultees have stated that the poor results described by De Andres alone suggest the trial was flawed and therefore the study should be excluded. Additionally, some consultees have implied that individual sources of bias, when considered collectively, are also grounds for exclusion. The EAC considers that these are logical fallacies, and instead close examination of the respective methodologies and settings are required to understand the differences in results. However, in the absence of published patient-level data from either the SENZA-RCT or De Andres study, it is not possible to replicate and reach any conclusions on these differences.

After extensive review of the issues discussed in Table 1, the overriding opinion of the EAC remains as stated in the first advisory report [2], that most can be explained by the poor reporting quality of the De Andres RCT, which made it confusing to read and occasionally appeared to present inconsistent statements. Reasons for the poor reporting quality may be related to its independent status and the fact it was designed to be pragmatic, rather than explanatory in nature [15]. In contrast to the SENZA-RCT, which was required for FDA PMA approval (section 4.2), there was no requirement to meet FDA reporting standards. Additionally, it is possible that some information was lost or distorted in translation (from Spanish to English). Nevertheless, the study appears to have fallen short of GCP in some instances, such as obtaining written patient consent. These issues are a concern, but in the opinion of the EAC, do not preclude the study from inclusion in the evidence base for NICE assessment. The EAC is satisfied the De Andres study reported on the other themes in Table 1 honestly, if in a confusing manner. In short, the EAC considers the study was well-

intentioned, but sometimes poorly executed and was consistently poorly reported. However, the EAC would not support the studies exclusion from the evidence base for NICE assessment unless definitive evidence of trial misconduct came to light. This would seem unlikely, since the Editor-in Chief of *Pain Medicine* has confirmed that the study is not under investigation [16]. It would be unacceptable for a study of this nature to be excluded largely on the basis of competing commercial interests or solely because conflicting results have been reported compared with the extant evidence base.

Compared with the De Andres study, the SENZA-RCT was commercially funded and tightly controlled, and, in general, was better reported. The EAC is now satisfied that the investigators had made reasonable attempts to reduce bias in certain domains (such as in the comparator arm) and there were no specific personal financial issues for the PI, potentially influencing the study. The results from the SENZA-RCT were more positive for both arms than the De Andres study, and showed superiority of Senza HF10 over a conventional LF SCS device in pain reduction. It should also be recognised that these results were not reported in isolation, and were largely supported by observational studies included in the company submission of evidence to NICE [17]. The most important of these were the SENZA-EU study (n = 83) [18, 19], the retrospective case series by Russo (n = 256) [20], and the observational study by Al-Kaisy *et al.* (n = 21) [21] in surgically naïve patients [19], which now has reported sustained efficacy at 3 years [22]. These studies are all limited by the fact that they did not have a comparator arm, and, being observational in nature, would have been subject to patient selection issues and confounding. Nevertheless, the longitudinal efficacy data in pain relief reported in the observational studies matched the profile reported for Senza HF10, showing similar reduction in pain over time compared with baseline.

There therefore remains a need to explain the differences in results between the De Andres RCT and the rest of the body of evidence for Senza HF10 therapy. The De Andres study was a small single centre study, and, as discussed, was poorly reported. In particular, the patients enrolled into the study were poorly described. Although they had similar basal pain scores as reported in other studies, the aetiology and nature of the pain was inadequately reported. Compared to those enrolled in the SENZA-RCT, the patients in De Andres appear to have lower levels of disability. Patient heterogeneity is also likely to play a role in both studies. Another important potential issue was the application of the intervention (Senza HF10) and the comparator, which may have been suboptimal. The role of non-specific treatment effects (placebo), which have recently been reported as being substantial in another SCS technology [23], is also unclear. This may have been related to the pragmatic nature of the study, with diminished expectations partly explaining the poor responses observed in both arms. However, at present all these potential explanations remain speculative. Finally, an issue with the De Andres study was its use of statistical analysis. Because the paper was poorly written, and because patient-level data are not available (also true for SENZA-RCT), it has not been possible for the EAC to fully interpret what the absolute and relative effects on pain were. This makes it difficult to compare results with certainty with results from other studies.

Some consultees made criticisms about the relative weightings of the studies in the overall assessment of the evidence base for Senza HF10 therapy. For clarity, the EAC does not believe that the study by De Andres is superior to the SENZA-RCT, nor did it apply any weighting to its assessment, explicit or otherwise. Rather, the EAC changed its initial opinion from the AR that there was “unequivocal” evidence (i.e. without doubt) for superiority of Senza HF10 therapy. The EAC maintains its opinion that the lesser degree of pain relief reported by De Andres has not been satisfactorily explained to date; therefore the published evidence is equivocal.

When considering the claimed superiority of Senza HF10, MTAC will consider the overall evidence base for the technology. On the one hand, superiority is evidenced by a larger, better reported trial in the SENZA-RCT, and this in turn is supported by complementary evidence from observational studies. However, there is a significant risk of bias in all these studies. On the other hand, a smaller, independent RCT has reported that Senza HF10 therapy produces similar pain relief outcomes compared with conventional LF SCS treatment in the De Andres RCT. This study is also subject to bias and is not corroborated by additional observational evidence at the present time. On the balance of probabilities, it would seem likely to the EAC that Senza HF10 therapy provides greater pain reduction than conventional LF SCS in appropriately selected populations. However, because of the De Andres study, this is no longer supported by the complete current evidence base, taken as a whole.

Finally, as concluded by the EAC in the first advisory document [2], other patient benefits associated with Senza HF10 therapy, such as eliminating paraesthesia, and therefore allowing patients to drive, are unchanged by the publication of the De Andres RCT.

3.2 CONCLUSION

The EAC has reviewed the public consultation comments on MTCD2, concerning the conduct and methodology of the RCT by De Andres *et al.* [3]. In the opinion of the EAC, this was a well-intentioned study that was poorly executed and reported. The EAC does not consider that any of the criticisms, individually or collectively, warrant its exclusion from the evidence base for NICE assessment of Senza HF10 therapy.

Definitive reasons for the conflicting results between the De Andres RCT and SENZA-RCT have not been identified, but may be partly related to differences in the population or pragmatic versus controlled application of technologies [5]. Without access to patient-level data, direct comparisons between the studies are not possible. Taking the evidence base as a whole, the likelihood appears to be that Senza HF10 therapy provides greater pain reduction than conventional LF SCS in appropriately selected patients. However, the evidence is not unequivocal.

Finally, the EAC would draw attention to the protocol of an NIHR-funded, UK, multi-centre, sham controlled trial that is due to start in August 2018 and complete in August 2020 (NCT03470766) [24]. This study is designed to address many of the current uncertainties in the evidence base for Senza HF10 therapy.

Section 4: EAC notes on Table 1

4.1 STUDY DESIGN

The SENZA-RCT [6, 7] was a pivotal multicentre study submitted to the US Food and Drug Administration (FDA) as part of product licensing in the USA. It was designed as a non-inferiority randomised controlled trial (RCT) but reported superiority results secondarily, which is methodologically acceptable [8]. There is no controversy about this.

Some consultees have questioned whether the De Andres study was in fact designed and implemented as a parallel prospective RCT, as reported. This scepticism seems to have largely arisen from the presentation of a poster at the International Neuromodulation Society (INS) meeting , held in Edinburgh in May 2017, with an abstract published in the journal *Neuromodulation* in October 2017 [25]. MTCD2 consultees have queried whether this cohort of 24 patients with failed back surgery syndrome (FBSS) implanted with Senza HF10 were the same as those described in the RCT, and if so, whether concurrent enrolment of the control group, receiving low frequency spinal cord stimulation (LF SCS), occurred.

The De Andres study described itself as a "Prospective, Randomized Blind Effect-on-Outcome Study" in its title, and in the methodology stated "This study was designed as superiority trial to verify that a new treatment is more effective than the standard treatment from a statistical point of view and from a clinical point of view" [3].

Matters of study history and design of the study were covered in the questions to De Andres in the Letter to the Editor by North and Eldabe [5]. Answering question 2, when asked directly, De Andres states "Yes, the study was conceived from the beginning as a prospective randomized controlled trial". De Andres goes on to state in response to question 5 that "preliminary interim data from a group of patients in the HF [high frequency] group that at the time of the INS deadline were available and had finished follow-up. Collection was done as part of the study, but analysis was done separately and with different statistical methodology from the main study, with its two groups". This appears to be have satisfied North and Eldabe who state in their summary "this RCT was intended as such and designed as an RCT from the outset". They do, however, agree that publishing patient data prior to the publication of the main study is often discouraged by journals and deferred on this point to the Editor-in-Chief of *Pain Medicine*. The EAC has since contacted the Editor-in-Chief, who confirmed "Pain Medicine has no plans for further action on the De Andres et al 2017 paper following the detailed and extensive review as outlined by Drs. North and Eldabe" [16]. The EAC would add that reporting of preliminary results at conferences is a common practice, especially for independent studies.

Another criticism of the De Andres study was that it was set in a single centre, as opposed to the SENZA-RCT that was multi-centre. Whilst single-centre studies have been claimed to be at greater risk of bias [26], they are commonly performed during evaluation of medical technologies, and the EAC does not consider this as a major source of bias or limiting factor in generalisability.

The EAC's conclusion is therefore there is no doubt that the De Andres study was a prospective RCT as described. It may be noted that if this were not the case, *all* the authors of the study (De Andres, Monsalve-Dolz, Fabregat-Cid, Villanueva-Perez, Harutyunyan, Asensio-Samper, and Sanchis-Lopez)

would be conspiring to commit fraud. Without further evidence to support this, such accusations may be considered defamatory.

4.2 REGULATORY BODIES, CONDUCT, GCP AND REGISTRATION

The SENZA-RCT was carried out in part to gain premarket approval (PMA) with the US Food and Drugs Administration (FDA) [27]. It was classified as a pivotal study meaning "a definitive study in which evidence is gathered to support the safety and effectiveness evaluation of the medical device for its intended use". It's adherence with good clinical practice (GCP) and other regulatory controls was not reported, but may be assumed because of the FDA oversight. The study protocol was registered on clinicaltrials.gov (NCT1609972) [28], although the EAC did note some discrepancies in the information presented compared with that of the published trial [1].

The following are extracts from the study by De Andres *et al.* (2017) [3]:

> "Approval was obtained from the Research Commission and the Clinical Research Ethics Committee of the Department of Health of Valencia General Hospital, Valencia, Spain, and the project was reviewed by the Spanish Regulatory Drug Agency (AEMPS) and classified as a "study with products for healthcare use.""

The authors continue to state:

> "The study complied with local regulations, Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and the applicable law and regulations governing personal data protection and rights and responsibilities regarding information and documentation in health care".

These facts were accepted on face value by the EAC at the time of writing the advisory document for NICE (Jan 2018) [2]. In their letter to the PI of the trial (Dr Jose De Andres) in April 2018, North and Eldabe [5] relayed enquiries from members of the neuromodulation community that the study did not adhere to expected standards of GCP or regulatory compliance. In the letter, it was established that only verbal consent for study participation was obtained, which may be considered a breach of GCP. In other areas of regulation, potential breaches of code were less clear, with North and Eldabe summarising that:

> "Questions of propriety and compliance with applicable regulations, which vary from one country to another, have been raised …... We rely on the authors' statements above to the effect that registering the study with public databases was not required, that notification to Spanish regulatory authorities and local ethics committees proceeded as described, and that informed consent for this randomized study was obtained verbally. Perspectives on these practices will vary by jurisdiction and perhaps by individual."

As a result of these issues, in particular the lack of written consent, some consultees have argued that such a fundamental issue with GCP should invalidate the study and lead to its exclusion from the evidence base assessed by NICE. This point needs to be resolved, possibly via deliberation at MTAC. Regarding the regulatory considerations, the EAC does not have adequate knowledge of the Spanish medical research landscape to assess whether any major breaches of code or practice occurred during the De Andres study (2017) [3].

The EAC had noted in the advisory document [2] that the De Andres study was not published in a trial protocol database such as clinicaltrials.gov or the ISCRCTN registry, and thus was not identified

by the EAC as a planned or on-going study during authoring of the original Assessment Report (AR) [1]. Not publishing the protocol for an RCT is considered a significant weakness and makes the study particularly prone to reporting bias. There has since been some suggestion that De Andres *et al.* had avoided publishing a protocol because it was not a statutory requirement and they "were concerned about heightened attention by manufacturers to care and programming of study patients, potentially affecting outcome, and this informed the design and conduct of the study" [5]. However, this does not appear to be justified to the EAC. The EAC would also agree with one consultee who stated the trial did not fully conform with CONSORT (Consolidated Standards of Reporting Trials) principles. These issues expose the De Andres trial to considerable risk of reporting bias, although the EAC has not identified an ulterior motive which would disproportionately affect either technology.

In conclusion, the authors of the De Andres study (2017) [3] clearly stated in their paper that the trial was conducted with full regulatory approval and with GCP. Upon further investigation, instigated by the neuromodulation community and investigated by the editors of the paper, it has transpired there were clear issues with GCP and possibly, less clearly, compliance with Spanish and EU regulation. As it is normally assumed that GCP, compliance with regulatory bodies and adequate clinical governance, have been undertaken before publication of an RCT in a peer reviewed journal, these issues do not form part of most critical appraisal tools, such as the *Cochrane Collaboration's tool for assessing the risk of bias in randomized trials* [29], used by the EAC. Hence the implications for study bias are unclear.

4.3 BLINDING

The issue of blinding, in an attempt to reduce bias, is particularly pertinent to treatments of pain conditions, including neuromodulation, because pain reduction has been observed to be particularly susceptible to the placebo effect [30].

The SENZA-RCT was entirely open label, with no attempt to blind patients, clinical staff, assessors, or evaluators [6]. Although blinding of patients was not possible (because of perception of paraesthesia), blinding of assessors and investigators would have been possible, although technically difficult. The SENZA-RCT did not report any measures on how expectation bias may have been reduced.

Several consultees claimed the De Andres RCT was not in fact blinded but was fully open-label, and the EAC was mistaken for describing it as blinded. It was suggested that "Only the clinical personnel who collected patient self-reports" were unaware of treatment allocation.

The EAC's belief that the trial was truly single (assessor) blinded was based on the following:

- It was described as such in the title.
- In the abstract it is stated "Design. Prospective, Randomized *blind* trial".
- In the methods it was stated "The evaluators who collected pain ratings and other outcome measures were blinded to the subjects' group allocations throughout the process. As such, they were disinterested third parties who were not involved in patient care at any time during the study process". The EAC notes that the primary outcome measure, the numerical rating score (NRS) for pain is communicated verbally [31], and so the blinded assessor would have actual contact with patients, and did not just collect forms. This would likely be true for some of the other outcomes reported too.

- The author drew specific reference to the importance of the blinding in their discussion, stating "We made a special effort to reduce observer bias by blinding outcome evaluators, who can be considered disinterested third parties".

Although not blinding *per se*, the authors of the study also made additional attempts to minimise bias with the following actions:

- Introducing the study to patients by “informing them that there were two groups and that treatment was equally effective in both”. This may reduce expectation bias.
- Removing the influence of clinicians where possible such as during device implantation, evidenced by “The same clinician placed the implants in all the study subjects, but did not take part in any further assessments” and Stimulation Parameter Programming , stating “All programming sessions were run by a team comprising a staff physician not involved in the implant process or in-patient follow-up”.
- Employing an independent statistician: “statistical analyses were designed and performed by an independent biostatistician”.

The EAC considered that these actions, combined, could plausibly reduce bias in the blinding domain only (detection bias). Nevertheless, although the EAC concluded the study was assessor blinded, in the Advisory document we were sceptical about the importance of practicalities of maintaining this masking and its importance in reducing bias [2]. Specifically the EAC stated “there may have been practical issues with maintaining blinding, and the subjective nature of the reported outcomes meant that cognitive bias from the patient in their pain assessment would have remained a major source of uncertainty”.

In summary, for the reasons stated, the EAC trusted that this was a single assessor blinded RCT, as described, and considered the study was methodologically superior to the SENZA-RCT *in this domain only*. Nevertheless, the EAC was sceptical of the importance of this form of blinding in reducing bias.

4.4 POPULATION

There have been some concerns from consultees that the population treated in the De Andres study may not have been representative of those likely to benefit from Senza HF10 or LF SCS (this criticism was also made of the SENZA-RCT in MTCD1, particularly regarding lack of neuropathic tests). In particular, consultees commented that the underlying cause of FBSS was not reported; that the patients in the Senza HF10 arm may not have had genuine neuropathic pain, as indicated by the basal Pain Detect Questionnaire (PD-Q) and lack of reporting of Douleur Neuropathique 4 (DN4) score; and that the disability scores, for example the Oswestry Disability Index (ODI) were substantially lower than seen in other studies (hence patients may have had less scope to benefit).

The EAC highlighted the population in the De Andres study was poorly described and stated with respect to generalisability “However, the population characteristics in the De Andres study are otherwise relatively poorly described, so there is some uncertainty concerning generalisability of the two populations” [2]. The baseline characteristics of the population in the De Andres study only reported Age, gender, FBSS status (100%), baseline pain (NRS), Pain detection questionnaire (PD-Q), and Oswestry Disability Index (ODI). The quality of pain was described, however, as “Pain was mainly axial low back pain or radiating leg pain that failed to respond to other treatment options”. As a pain centre as part of a teaching hospital, it might be assumed that patient selection should appropriately reflect internationally recognised clinical practice, but this is not certain.

Age, gender and baseline pain scores at baseline appear to be very similar in both studies. The SENZA-RCT did not report PD-Q scores. Although it is difficult to compare ODI scores with those reported in the SENZA-RCT, as De Andres used mean scores whereas Kapural reported proportions of patients in categories (minimal, moderate, severe, and critical), it would appear that patients enrolled into the De Andres study had significantly less disability, which could help explain discrepancies in results.

In conclusion, participants in both trials were insufficiently described at baseline to ascertain their generalisability to the decision problem with certainty. Reporting of patient characteristics was worse in the De Andres study, particularly concerns the underlying cause of pain and level of disability. Differences in populations may partly explain some of the differences in results reported.

4.5 INTERVENTION

Several consultees have queried if the intervention (Senza HF10 therapy) was employed correctly in terms of lead placement and stimulation parameter programming, and indeed some queried if it was used at all (e.g. MTCD2 comment 15). From the De Andres paper the following statement was made about implantation (*EAC emphasis*):

> "In the HF group, two percutaneous leads with eight electrodes were implanted. The end tip of one of the leads was placed at T8 and the other one at T9, both near the anatomical midline. The leads were placed in such a way that the electrodes were staggered at T9 in order to achieve coverage in the T8-T11 segment with all 16 electrodes. The leads were connected directly to a rechargeable impulse generator (*Senza System, Nevro Corp., Menlo Park, CA, USA*)". And "Correct positioning of the leads was confirmed using anatomical landmarks".

The EAC thought this description appeared consistent with other descriptions of lead implantation from other studies and reviews. However, the EAC does not have the clinical expertise to query the radiographic image presented in Figure 1 of the paper, which was an issue with some consultees. At the time of writing (14th June 2018), four clinical experts had responded to a prepared question on lead positioning, with one of these deferring opinion to other experts as they had no hands on experience of the technology (see MT330 Senza SCS NY EAC external correspondence log [16]. The responses were as follows:

- Expert 1: "Figures are just that and cannot be taken as gospel. I appreciate that in the printed version the positive and negative signs are a bit off centre from the T9/10 interspace but suspect this is a journal issue and thus they are generalisable in my view".
- Expert 2: "Lead placement in the illustration is lower than the clinically proven optimum for HF10 therapy".
- Expert 3: "NO. The leads are NOT in the midline and are not staggered. Generally the leads are placed in the midline from T8-T11 with staggering of the leads to enable coverage across the T9-10 disc space".

The following statement was made in the paper concerning programming:

> "Pulse width: *The initial pulse width was 30 µs. If the patient had good coverage except for a small percentage (toe, lower back), pulse width was increased*. 3) Amplitude: Minimal initial amplitudes were always 1.5 mA, whereas maximal amplitudes were 5mA and always adjusted to obtain the optimal analgesic response. 4) Frequency: 10,000 Hz".

There were concerns about the statement in italics, in that it might not be possible to adjust the pulse width in this way whilst maintaining 10 kHz frequency, and anyway, as Senza HF10 is paraesthesia free the patient cannot sense coverage. This has since been confirmed by Nevro (see MT330 Senza SCS NY EAC external correspondence log [16]. The three clinical experts responded as follows:

- Expert 1: "to increase pulse width, and reduce frequency to a paraesthesia mode if the above as well as cathode relocation change has not worked (this is done on occasion to target HF10 therapy although rarely in my experience. The whole programming section is unfortunately badly written and could have been expressed better but given that the devices were programmed by industry representatives in both arms, it was my opinion that the way the text is worded would have no impact on the final outcome data .Hence why this was not addressed in our letter or the editorial that preceded it".
- Expert 2: "I asked Nevro about the pulse width and I was told that it cannot be raised above 30mcs. The comment about "coverage" shows that low-frequency stimulation must have been employed in testing, as HF cannot be felt and coverage is in any case widespread".
- Expert 3: "YES. With HF10 therapy the stimulation is paraesthesia free. Yet the author states that the pulse width was increased if the coverage was not good. You shouldn't be testing coverage as the therapy is paraesthesia free"

From these three responses, regarding lead placement, the EAC considers there is some uncertainty whether lead placement was optimal. However, this is on the basis of limited clinical feedback on a single radiograph in Figure 1A of the paper (there does not appear to be controversy regarding the narrative of Figures 1 B and C). It is unclear how many, if any patients were affected by suboptimal lead placement.

Regarding stimulation parameter programming, clearly this is poorly reported in the paper, but the EAC thinks it is most likely that, in some patients, the Senza device was optimised by temporarily switching to low frequency to ascertain coverage and efficacy at the time of assessment only. This could have been done following the trial and at programming sessions throughout follow up in selected patients who require it only, and may reflect pragmatic nature of the study. The number of patients potentially affected is unknown. The EAC is relatively confident that the Senza HF10 device was set appropriately in 10 kHz mode during the periods between follow up time points, and there was no evidence cross over occurred between frequencies. It is also important to note that the programming of Senza HF10 and Medtronic devices were undertaken by a team including company representatives, which should reduce the potential for inappropriate application of these technologies.

In addition to feedback the EAC sought directly from the company and clinical experts, NICE passed some additional correspondence from Nevro Corp. concerning the implementation of Senza HF10 therapy in the De Andres study (Appendix Two). The EAC has reviewed this document at NICE's request and considers the points made do not raise any additional substantive issues concerning the conduct of the trial or the implementation of Senza HF10 in the trial.

In conclusion, the De Andres study was poorly reported (possibly relating to translational issues) and it is possible that application of either or both technologies was suboptimal, both at unknown time points and for an unquantified number of included patients in the study. However, as programming was undertaken in the presence of company representatives, as described in Appendix Two, this

should allay fears that the intervention was applied entirely inappropriately for all patients and at all times.

4.6 COMPARATOR

In the SENZA-RCT, it was not reported who performed the intra-operative programming of the LF SCS device (the Precision Plus System [Boston Scientific, USA]) [6], which the EAC had considered to be a potential source of bias. However, during consultation it has been reported that in fact programming was carried out by an employee of Boston Scientific, who would be clearly incentivized to achieve the best results possible with the device. The EAC therefore would not consider the programming of the comparator to be a source of bias in this study.

In the study by De Andres it is reported that "All programming sessions were run by a team comprising a staff physician not involved in the implant process or in-patient follow-up and by a *representative of the device manufacturer*". Again, this would be expected to reduce the potential for performance bias.

In conclusion, the EAC was satisfied that neither study was particularly prone to bias in the comparator domain.

4.7 OUTCOMES

The EAC had noted in its Assessment Report [1] that the primary outcome of the SENZA-RCT [6] was pre-specified in the trial protocol published in ClinicalTrials.gov (NCT01609972). Whilst some inconsistencies were noticed, for instance regarding predicted sample sizes, overall the EAC were satisfied the non-inferiority design (with post hoc superiority testing) had been appropriate and recognised that the primary outcome (proportion of responders) reflected those of previous studies [12, 13]. Additionally, this outcome partly informed cost utility analysis (not performed for this guidance).

In comparison, the reporting of outcomes was less satisfactory in the study by De Andres [3], with the EAC drawing attention in the first advisory document [2] to the lack of rationale and basis for determination of the sample size; the lack of a pre-specified hypothesis to be tested; the absence of reporting of the primary outcome; and lack of discrimination in pain scores between leg and back pain. Additionally, the follow up periods were confusing (see Section 4.8), denominator data were often missing, intention to treat analysis was probably not carried out, and neither was statistical adjustment for multiple comparisons.

Neither study adequately published individual patient data, either in the body of the text or as supplementary material (although the SENZA-RCT did illustrate individual patients graphically [7]). Ultimately, this meant that, when comparing studies, the EAC was only able to provide a narrative and graphical comparison of longitudinal data, rather than a statistical analysis. However, De Andres did clearly show a lack of superiority of Senza HF10 compared with LF SCS which contrasted with the results for the SENZA-RCT. Similar findings were reported for the other outcomes. Recently, additional patient orientated data have been published from the SENZA-RCT [10] (Appendix One). This reported that Senza HF10 therapy was associated with improvements in a range of outcomes compared with LF SCS (listed in Table 2). However, improvement in generic QoL was not found.

In conclusion, the SENZA-RCT had superior reporting quality compared with the De Andres study and should probably be considered to be at lower risk of reporting bias. It reported a significant reduction in pain relief for both technologies compared with baseline, and also superiority of Senza HF10 compared with LF SCS in pain relief and several secondary outcomes. In comparison, the study

by De Andres was poorly reported, but did not report evidence of superiority in favour of Senza HF10. Despite the poor reporting of outcomes in the De Andres study, the EAC does not believe this should be discounted; rather, this adds additional uncertainty when interpreting the results of this study.

4.8 TRIAL

Several consultees commented that the data reported in the study by De Andres indicated that patients who did not achieve the full 50% reduction in NRS pain at trial phase were accepted inappropriately for permanent implantation. This has led the EAC to scrutinise the reporting of this in detail.

The EAC has previously advised (January 2018) that the De Andres RCT was poorly reported, with an absence of patient-level detail in the results. This poor reporting extends to the presentation of results in Table 3 of the paper, where denominator patient numbers are not given and the actual measurement time points (particularly t1 and t2) are not adequately specified. The pain results (NRS scores) in Table 3 are reported as absolute aggregate means with standard deviations (SD), or differences in these. Consultees were concerned that the figures reported for NRS at t1 and t2 were less than the 50% minimum pain relief expected between baseline and first follow up. Therefore, the EAC has undertaken mathematical simulations to test if Table 3 reports the randomised cohort at t1 (n=60), i.e. if these baseline results include those who had an unsuccessful trial in Figure 2 (n = 31 CF and n = 29 HF). The results of these simulations demonstrate that it is, mathematically, highly improbable that the Table 3 results include the 5 patients who failed the trial phase.

In the absence of patient-level data to analyse and replicate results, the EAC infers it more likely that the De Andres paper is written in chronological order and that the 3/29 unsuccessful HF trial patients and 2/31 unsuccessful CF trial patients are not reported after the first two paragraphs of the Results section. We believe that Table 3 reports *only the patients proceeding to permanent implant* (n=55). Hence we infer that the t1 described in the Letter to Editor (North and Eldabe, April 2018) as "refers to basal data obtained at the time of inclusion in the study" means for n=55 permanently implanted patients only. This inference is supported by the results reported in the narrative of the paper under the "Numeric Rating Scale "subheading, which are comparable to the ranges presented in Table 3.

Furthermore, the Pain Detect Questionnaire (PD-Q) mean baseline value of 16.23 in the HF group (implanted) would be "unclear" rather than "unlikely" to have neuropathic pain, but at the upper end of the NeP scale (13 to 18).

In conclusion, the EAC believes that patients were appropriately entered from trial to permanent implantation, but this was poorly reported.

4.9 FUNDING

The De Andres study stated the following "Funding sources: None. This study was not sponsored by any device manufacturer. The investigators took care to minimize the role of manufacturers' representatives in device adjustment and patient management". It goes on to state the study was "funded from our departmental resources" [3]. Nevro Corp. was unaware of the study, but has clarified to NICE that their operators were involved in programming of the device, under instruction from the clinicians, as they are for all device implantations (see Appendix Two).

The SENZA-RCT was funded by Nevro Corp, which was highlighted in the first Advisory document produced by the EAC [2]. The EAC had stated in its Advisory document that "Although this is a

general issue, it is widely accepted that industry-sponsored studies, *where principal investigators have financial ties to the technology*, are associated with more positive results than independent studies". Attention was drawn from consultees that the PI of the SENZA-RCT, Leonard Kapural, did not have financial ties to Nevro. The EAC is therefore happy to clarify its statement was meant as a general point only and not to insinuate Dr Kapural was personally gaining financially through the trial and trial results.

Thus, although the EAC maintains that, as a general issue commercially funded trials are prone to report excessively positive results, the EAC does not now have specific issues with the conduct of the SENZA-RCT trial in this regard. The study by De Andres should be unaffected entirely by such sources of bias.

Appendix One: Review of Amirdelfan *et al.* (2018)

The study by Amirdelfan *et al.* ("Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT") was accepted for publication on May 22nd 2018, the day after the deadline for comments for MTCD2 [10] and published online first on June 1st. This study reported tertiary outcomes from the SENZA-RCT [6] pertaining to patient related outcome measures (PROMs), functional outcomes, and quality of life (QoL). No new patients were reported and follow up was 12 months. These outcomes had been specified in the Summary of safety and effectiveness (SSED) for Senza HF10, submitted to the US Food and Drugs Administration (FDA) and some were included in the company submission of evidence to NICE, as unpublished data.

The SENZA-RCT has been appraised previously by the EAC in the Assessment Report [1], and the strengths and limitations of the study described previously also apply to this study. However, not all the patients reported all outcomes, indicating that intention to treat analysis had not been applied, and there was additional potential for attrition bias. The outcomes reported appear to be concordant with those stated in the SSED, which should limit reporting bias, although the lack of pre-specified hypotheses and choice of statistical analysis could have led to a degree of bias in this domain. Some of the outcomes had previously been reported in the SENZA-RCT [6, 7], whereas some were newly reported. All outcomes were reported at baseline and 12 months, and statistical analysis was performed longitudinally (before and after) and comparatively (between Senza HF10 and conventional low frequency spinal cord stimulation [LF SCS]). It is unclear why the new data were published some 30 months subsequent to the seminal SENZA-RCT paper [6]. The results of this study are reported in Table 1 of this second advisory document.

In terms of longitudinal data (comparison with baseline), both Senza HF10 and LF SCS were associated with significant improvements in functioning and reduction in disability. However, the study reported that Senza HF10 was superior to LF SCS in several outcomes, including the Oswestry Disability Index (ODI); Short Form McGill Questionnaire 2 (SF-MCQ-2); and Patient and Clinician Global Impression of Change (CGIC and PGIC). Longitudinal improvements in sleep quality and the ability to drive using Senza HF10 were also reported. Some of these results had been published previously, and overall these results are consistent with the original data reported from the SENZA-RCT [6], which reported a significant large and sustained reduction in pain associated with Senza HF10 compared with LF SCS.

One important outcome that did not report superior results for Senza HF10 was in generic health related quality of life, as measure by the 12 Item Short Form Survey (SF-12) [32]. Comparative analysis reported no significant improvement in the mental or physical composite scores (individual components were not reported). The authors speculated that the sample size might not have had the required sensitivity to detect a difference. However, the differences in point estimates were small, indicating the difference between technologies might not be clinically important for this endpoint. This outcome was also measured by De Andres *et al.* (2107) [3], who also reported no significant difference in composite scores (mental or physical). In contrast, Al-Kaisy *et al.* (2016) had

reported significant improvements in SF-36 mental and physical component scores in a single-armed trial in patients naïve of back surgery [21].

In summary, the study by Amirdelfan (2018) provided additional evidence that Senza HF10 may result in improved PROM outcomes compared with LF SCS, subject to the same caveats as the Senza HF10 study [6]. However, the study did not detect a difference in generic health-related quality of life between the technologies.

Table 2. Summary of results from Amirdelfan *et al.* (2018).

Outcome and description	Reported previously?	In scope?	Statistical analysis	Longitudinal results	Comparative results (Senza HF10 vs LF SCS)	EAC comment
Oswestry Disability Index (ODI) [33] Self-reported questionnaire that measures functional disability in up to ten domains.	Yes, in SENZA-RCT [6], several observational studies, and company submission.	Yes, directly	Comparison of medians and proportions in subcategories. Mann-Whitney U test.	Both LFSCS and Senza HF10 significantly improved at 12 months compared with baseline.	Significant improvement in median ($p = 0.016$) and subcategories ($p = 0.01$)	SENZA-RCT also reported 24 month data [7].
Global Assessment of Functioning (GAF) Numeric scale subjectively rating social, occupational, and psychological functioning [34]	Yes, in SENZA-RCT [6], Al-Kaisy (2015) [35] and company submission	Yes (functional disability measure)	Comparison of medians and proportions in subcategories. Mann-Whitney U test.	Both LFSCS and Senza HF10 significantly improved at 12 months compared with baseline.	5.0 improvement in median ($p < 0.01$).	No significant comparative improvement reported in SENZA-RCT [6].
Short Form McGill Questionnaire 2 (SF-MCQ-2) [36] Assessment of major symptoms of both neuropathic and non-neuropathic pain	No	Yes (pain score)	Comparison of medians. Mann-Whitney U test.	Reductions in all components of pain compared with baseline	Significant reductions in continuous ($p < 0.005$), intermittent ($p < 0.005$), and neuropathic pain ($p < 0.01$) No significant difference in affective disorder ($p = 0.080$)	The SF-MCQ-2 provides a more detailed description of the type of pain. However, it has not been widely used in other studies of SCS.
12 Item Short Form Survey (SF-12) [32] Generic quality of life reported as mental and physical composite scores	No (although SF-36) reported by Al-Kaisy (2015) [21]	Yes, directly	Comparison of medians. Mann-Whitney U test.	Improvement in both mental and physical scores reported in both groups, but statistical significance not reported	No significant difference between technologies.	This outcome was not reported in initial publications [6, 7]. SF-12 scores are important in determining overall improvement to quality of life. SF-12 was also reported by De Andres (2017) [3] but no significant differences between technologies reported.
Patient and Clinician Global Impression of Change (CGIC and	Yes, in SENZA-RCT [6] and company	Yes (functional	Comparison of categories.	N/A	Non-significant improvement in PGIC	Significant improvement in both PGIC and CGIC at 12 and 24 months

Outcome and description	Reported previously?	In scope?	Statistical analysis	Longitudinal results	Comparative results (Senza HF10 vs LF SCS)	EAC comment
PGIC). Measure of symptom severity and treatment response	submission.	disability measure)	Fisher's exact test		(p = 0.052) Significant improvement in CGIC (p = 0.009)	previously reported [7]
Sleeping and driving questionnaire	Reported in submission (unpublished)	Indirectly (patient satisfaction, adverse events, functioning)	Fisher's exact test	N/A	More patients left device on whilst sleeping and driving (both p < 0.001)	Not included previously in Assessment Report because data were not published in a peer-reviewed journal. Not a validated measure.
Pittsburgh Sleep Quality Assessment (PSQI) [37] Self-rated sleep measure (19 individual items generate 7 component scores)	No	Indirectly (quality of life, functional disability)	Fisher's exact test	Improvement in proportion of "good sleepers" from baseline in Senza HF10 group only (p = 0.01)	No difference reported.	Other sleep measures (unpublished) were reported in submission.
Reliance on patient remote programmer (optional survey)	No	No	N/A	N/A	35.5% of LF SCS used remote controller daily, compared with 0% for Senza HF10	Optional, non-validated, survey.

Appendix Two: Letter to NICE from Nevro Corp.

Background Context:
The DeAndres publication was not registered under any data base and enrolment dates were not provided. Informed written consent was not obtained. What is particularly concerning is that 9 of the 10 patients with whom we have recently interacted deny knowing that they were ever in a study, that the device and surgery they received was due to a randomization process, or that they had regularly attended scheduled clinic visits and evaluations. Nevro was not aware of any study despite four years of routine patient interactions. We do not know if Medtronic was informed.

We contacted the relevant Ethics Committee (CEIC de l'Hospital General Universitari de València, 12/22/2017) and asked them to investigate requesting, as a minimum, to determine if there was indeed a protocol submitted for review and upon what date that review occurred. The Ethics Committee responded that they were concerned about *"the rights of the patients"* and that they would investigate and respond after their next meeting (26, January 2018). However, despite multiple follow up requests the committee has not provided any further information. For all these reasons, it is necessary to use sales data to determine possible dates of enrolment and the involvement of Nevro personnel.

We can verify from required documentation that devices sold to the Institution (General University Hospital of Valencia, Spain) for indications discussed in the publication occurred December 2012 (N=2), 2013 (N=12), 2014 (N=7), 2015 (N=6), 2016 (N=2 however 1 was explanted due to infection, yet no infections were reported in the publication). Devices implanted in 2017 could not have been included given that 12-month data with the same cohort was first presented as an observational, single arm study of Senza HF10 therapy at a congress in May 2017 (See: North, Eldabe, Letter to the Editor, Pain Medicine 2018; 0: 1–2 doi: 10.1093/pm/pny064). We do not have visibility on the Medtronic sales data; an inquiry by the MTEP could potentially verify if Medtronic sales in each of these years was approximately the same as would be required for a 1:1 randomization.

Thus, taking all this together we believe that the publication includes nearly all devices sold (at least 26 of 28) to the institution over a four-year interval beginning from the very first devices implanted by Dr. DeAndres in 2012 extending through to early 2016. Three of these patients required revision surgery due to lead migration: one in September 2014, one in July 2015, and one in November 2015. The time between observed loss of efficacy due to lead migration and revision surgery is not addressed in the article but obviously would have significantly impacted outcomes.

~~EAC~~ *[sic]* NICE question: *Would it be possible to confirm if there were any Nevro representatives involved in the De Andres study (e.g. assisting with programming) and if so, in what capacity?*

Nevro operates through a distributorship in Spain (PRIM, Madrid). These are commercial personnel who are trained and supported technically by NEVRO but also distribute other medical devices and products. Nevro maintains responsibility for product performance, safety and efficacy monitoring, regulatory records and data collection related to usage of our devices.

It should be noted that in both the SENZA-RCT and SENZA-EU and in the "Real World" clinical practice when optimal or sufficient pain relief is not realized, the patient would visit the clinic and be reprogrammed. It appears usual clinical practice was not followed in DeAndres study, as patients in both arms did not appear to achieve 50% pain relief at any time point. Furthermore, in the DeAndres study. HF10 therapy was applied initially but our treatment algorithm was not followed consistently.

Interactions between Nevro and agents for Nevro occurred in the standard way with the patients contacting the representatives to discuss treatment options and to request adjustments to the

device or with questions concerning operation of the device. While Nevro distributor representatives did have contact with the patients, actual programming clinic visits were arranged irregularly (not at fixed intervals of 1, 3, 6, 12 months).

While the clinic was provided a programing computer for a period of time during the assumed enrolment period, our records indicate that, when allowed to reprogram the device, it was performed by Nevro supplied personnel as directed by the supervising physicians at irregular times on an “as needed” basis.

Appropriate programming is dependent on recommended lead placement. HF10 therapy leads are placed anatomically in the midline from T8 to T11, not as depicted in figure 1 (A) on page 4 of the De Andres paper which instead shows standard paraesthesia based lead placement.

On a number of occasions including within the first 12 months from implant (that should have been included in the published article) programming records document that the Clinic personnel or implanting physician demanded that the patients be programmed with Low Frequency, paraesthesia based programs or other non-standard configurations to which our representatives necessarily complied.

In summary, it appears that Nevro distributor personnel were technically involved in programming although the supervising clinic personnel often deviated from recommended HF10 algorithm as studied in the SENZA-RCT.

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Errata to Advice on Senza HF10 SCS consultation comments

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INVESTORS IN PEOPLE

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The following changes are published as a supplement to the following two supporting documents from Newcastle and York External Assessment Centre (EAC):

- "Advice on Senza HF10 SCS consultation comments", 17th April 2018 [1] and
- "Advice on Senza HF10 SCS public consultation comments on MTCD2", 20th June 2018 [2].

These clarifications are made available by NICE to correct factual inaccuracies in the EAC advisory documents, arising from consultee feedback (changes made are highlighted in yellow).

Section 7.2.2 Table 8 (page 37) [1].

Table 8. *Estimates of explantation rates for conventional and non-conventional SCS and Senza HF10.*

Technology type	**Year**	**Company estimate (95% CI)*** **(n = 171)**	**Van Buyten (unanticipated explant for inadequate pain relief)** **(n = 955)**	**Van Buyten (unanticipated explant for any reason)† (n = 955)**
Conventional low frequency non-rechargeable	Year 1	[redacted]% ([redacted] to [redacted]%)[1]	3.6%	6.9%
	Year 2	[redacted]% ([redacted] to [redacted]%)[1]	3.9%	7.5%
	Year 3 onwards	3.2 (0 to 15.8%)[2]	2.8%	5.4%
Conventional low frequency rechargeable	Year 1	[redacted]% ([redacted] to [redacted]%)[1]	9.3%	17.8%
	Year 2	[redacted]% ([redacted] to [redacted]%)[1]	4.5%	8.6%
	Year 3 onwards	3.2 (0 to 15.8%)[2]	5.5%	10.6%
Senza HF10	Year 1	[redacted]% ([redacted] to [redacted]%)[1]	7.2%	13.8%
	Year 2	[redacted]% ([redacted] to [redacted]%)[1]	5.6%	10.7%
	Year 3 onwards	3.2 (0 to 15.8%)[2]	5.0%	9.6%

* Company estimate derived from patient level data from the SENZA-RCT (AiC). This was accepted by the EAC and MTAC for the base case analysis.
** Data reported by Van Buyten study (2017) ~~without extrapolation~~ [3]. Data for 1 and 2 years reported directly from annual data. Data for 3 years onwards calculated using time to event analysis (potential for bias).
† Data extrapolated from Van Buyten study, see **Section 3.3**.
1. Source: SENZA-RCT (unpublished data).
2. Source: Assessment report for TA159 [4].

Section 7.2.2 Table 9 (page 38) [1].

Table 9. Sensitivity analysis using explantation data from Van Buyten et al. (2017) [3] (15 year time horizon).

Data source	Cost Senza HF10 (£)	Cost conventional non-rechargeable SCS (£)	Cost conventional rechargeable SCS (£)	Δ Cost conventional non-rechargeable SCS (£)	Δ Cost conventional rechargeable SCS (£)
Company submission (base case)	87,400	95,156	92,196	**7,756**	**4,796**
Van Buyten (unanticipated explant for inadequate pain relief)	90,071	93,043	92,557	**2,972**	**2,486**
Van Buyten (unanticipated explanted for any reason)	95,837	95,485	98,128	**-352**	**2,291**

Abbreviations: SCS – spinal cord stimulation.

Green shows that Senza HF10 is cost saving. Red shows that Senza HF10 is cost incurring.

Explanation for erratum in section 7.2.2 [1]

The top row of table 8 and the bottom left column of table 9 should have emphasised that the explants were *unanticipated* rather than anticipated. That is, the devices were removed for a reason other than battery depletion. The "unanticipated explant for any reason" value was obtained by simple extrapolation of the published data reported in the Van Buyten paper using explantation for inadequate pain relief (which is a subset of unanticipated explantation rate for any reason, and for which the authors reported stratified data for each device type) and overall unanticipated explantation rate (which were not reported stratified data for each device type). This is just done by increasing the values by about 50% proportionately for all device types (Table 4, page 21 of [1]). Caveats to both this extrapolation and the original data source that Van Buyten reported are described (pages 17 and 38 of [1]).

This reflects that unanticipated explants are not solely due to inadequate pain relief. The main reasons for unanticipated explantation (other than inadequate pain relief) reported in the Van Buyten paper were infection (5%) and IPG failure (2%), followed by lead problems, pain at pocket, need for MRI, free of pain, and other (all <1%). The EAC's key assumption was that these events were independent of device type. Interestingly, dislike of paraesthesia was not cited as a specific reason for unanticipated explantation (but may have been in the "other" category). Using this value, Senza HF10 is approximately cost neutral compared with non-rechargeable devices (£23.40 more expensive per annum). The reason for this is because non-rechargeable devices have a lower *unanticipated explantation rate* than the rechargeable devices; Van Buyten speculates potential reasons in the conclusion of the paper.

Anticipated explantation rate refers mainly, or perhaps solely, to replacement of the device due to battery depletion. The EAC did not use this data from the study to inform the model. It was poorly reported and, in fact, Dr Van Buyten later confirmed in his consultation letter that the data only pertained to non-rechargeable devices. This makes sense, since the study limit was 6 years and all rechargeable devices should surpass this, but it was not made clear in the published paper.

Section 2 Table 1 (page 3) [2].

Domain*	SENZA-RCT	De Andres	EAC comment
Blinding[4.3]	The study was open label with patients~~, clinicians, assessors, analysts,~~ and investigators being aware of interventional allocation.	The study blinded clinical assessors who ~~made~~ recorded measurements on pain and disability metrics.	The EAC maintains the De Andres study was a single blind RCT, which should lower detection bias. However, the risk of unmasking would be considerable. Both studies would be at high risk of performance and other biases.

and the associated EAC notes on this table in Section 4.3 (Page 11) [2]:

"The SENZA-RCT was ~~entirely~~ open label, with no attempt to blind patients~~, clinical staff, assessors,~~ or ~~evaluators~~ investigators. Although blinding of patients was not possible (because of perception of paraesthesia), blinding of assessors and investigators would have been possible, although technically difficult. The SENZA-RCT did not report any measures on how expectation bias may have been reduced."

Explanation for erratum in Section 2 Table 1 and associated EAC notes in Section 4.3 [2]

The published SENZA-RCT study [5] states, *"Due to practical considerations (see Limitations section), study subjects and investigators were not masked to the assigned treatment group"*. There is no mention of assessors or evaluators in the published paper, nor if they were blinded. However, the SENZA-RCT Principal Investigator submitted a letter to NICE on 18/05/2018, during the public consultation on MTCD2, to state that *"Independent data collectors (disinterested clinic personnel) entered the patient level data into a locked data base."*

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KING'S HEALTH PARTNERS

Pioneering better health for all

KiTEC

MT330 – Senza HF10 evidence review

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Project Details

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Abbreviations

CI	Confidence interval
HF-SCS	High frequency spinal cord stimulation
ITT	Intention to treat
LF-SCS	Low frequency spinal cord stimulation
PP	Per protocol
SCS	Spinal cord stimulation
SR	Systematic review

1. Summary

The public consultation of the draft recommendations for the Senza HF10 therapy, raised the following concerns about the evidence assessment:

- Was the trial conducted according to European clinical trial standards with respect to ethical and regulatory considerations?
- Is the patient population clearly described and is it consistent with the patient population described in the decision problem?
- Was the trial planned as a prospective randomised trial? Was it adequately powered?
- Was the HF10 therapy intervention implemented and used in an appropriate way?
- Are all the primary and secondary outcomes adequately reported?
- Are the results consistent with other studies on spinal cord simulation?
- De Andres RCT
    - Was the trial fully or partially blinded? How could this have impacted the results?
    - Should this evidence be legitimately considered or not by the committee?
- SENZA-RCT
    - Was there potential bias introduced by the funding of the study?
    - Could patients be influenced by marketing material?
    - Were there any other forms of bias? If yes, how did this impact the results?

In response to these concerns, NICE requested KiTEC to assess the evidence associated with 2 of the RCTs included, the De Andres 2017 and the Senza RCT (for a full scope of the work requested by NICE please see appendix 1). KiTEC produced a brief report containing a review of the evidence and KiTEC's conclusions about the clinical effectiveness of Senza HF10. KiTEC also approached two clinical experts previously involved with the Senza HF10 therapy in clinical practice and in research based at the Chronic Pain Management and Neuromodulation Centre[1]. Combining the above information KiTEC concluded the following:

- The De Andres RCT does not have any clear methodological improvements over the SENZA RCT and the multiple shortcomings with regards to information governance

[1] Dr Al-Kaisy Adnan - clinical lead and consultant in pain medicine and neuromodulation and Dr Palmisani, Stefano - consultant in pain medicine.

requirements, inadequate statistical analysis and lack of transparency in various methodological aspects cast doubt on the accuracy of the reported results.

- The committee should disregard the evidence included in De Andres 2017 with regards to issuing guidance recommendations on Senza HF10 therapy.

2. General review

2.1. Was the trial conducted according to European clinical trial standards with respect to ethical and regulatory considerations?

According to the Clinical Trials Directive 2001/20/EC 'informed consent' is a ''decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation''. The requirement for written consent is applicable to trials of medicinal products as well as medical devices. Based on the response from the authors as provided to the Letter to the Editor (North 2018) only verbal consent was provided for participating to the study, therefore, violating the requirement as outlined in the Clinical Trials Directive.

2.2. Is the patient population clearly described and is it consistent with the patient population described in the decision problem?

Although the De Andres RCT paper states the inclusion and exclusion criteria, it provides little information on the baseline demographics and clinical characteristics. These were mainly limited to age and the ratio between men/women, and the average baseline pain measurements between the 2 groups. Other important information such as:

- the years since initial diagnosis (or duration of pain before SCS)[2]
- the use of opioid analgesics
- the morphine equivalent units

[2] With regards to the duration of pain before SCS; the SR and meta-analysis by Taylor 2014 showed that it was predictive of the level of pain relief following SCS.

- Separate reporting of pain measurements for back and leg pain

The populations included in the 2 RCTs (De Andres 2017 and SENZA-RCT) were similar to previous studies with SCS as reported in Taylor 2014[3] with regards to age, female/male ratio and baseline pain score. However, due to limited reporting of De Andres 2017, further conclusions on how representative the population in De Andres is to the broader population recruited in SCS studies is difficult to ascertain. *Table 1* below shows some of the population characteristics between the De Andres 2017 and SENZA-RCTs.

Table 1: Studies clinical characteristics intervention

	De Andres 2017	SENZA-RCT	Taylor 2014
Gender %	F = 42.3%	F = 62%	F = 48%
Age mean ± SD	51.62 ± 9.31	54.6 ± 12.4	50 (SD=NR)
% of pts with previous surgical intervention	100%	87%	[i]100%
Number of surgical interventions	NR	≥ 1	≥ 1
Time after surgery diagnosis (mean)	NR	13 years	7 years
Pain level prior to surgery (mean)	7.69	7.4	7.8
Pain characteristic	Axial low back or radiating leg pain	Axial low back or radiating leg pain	Axial low back or radiating leg pain
[i]Median from included studies, range 0-100			

According to multivariable analysis reported in Taylor 2014, with the exception of the duration of pain, no other characteristics (study-, patient- or technology-related) were seen to be significant

[3] Conducting a separate systematic review was outside the scope of this work, KiTEC used the systematic review from Taylor 2014 to provide information with regards to the broader population included in studies with SCS and the size of the effect reported from the literature for LF-SCS.

predictors of pain relief following SCS. Additionally, pain location was found not to be predictive of treatment outcome (Taylor 2014).

According to the scope, the population included in the Senza HF10 assessment report is patients undergoing SCS for chronic pain in line with NICE Technology Appraisal 159. According with the appraisal, SCS is recommended as a treatment option for adults with chronic pain of neuropathic origin who:

- continue to experience chronic pain (measuring at least 50 mm on a 0–100 mm visual analogue scale) for at least 6 months despite appropriate conventional medical management, and
- who have had a successful trial of stimulation as part of the assessment performed by a multidisciplinary team

Although the population included in De Andres had at least a minimum pain intensity of 5/10 on the numeric rating scale (NRS), the paper does not report the time duration between symptoms and attempts for previous management and the initiation of SCS treatment.

2.3. Was the trial planned as a prospective randomised trial? Was it adequately powered?

As the authors do not provide evidence of previous trial registration on a public domain it is difficult to ascertain whether the study was planned from the outmost as a prospective RCT. However, the following parameters strongly point towards the direction that this study was not prospectively planned:

- the publication does not report the recruitment and follow-up period as standard practice for prospective RCTs
- no information is provided on the method used for randomisation to ensure this was done effectively
- the patient baseline characteristics and demographics are underreported
- In 2017, a previous conference abstract from the same group reported an observational study which included the same patient cohort for the intervention
- according to the manufacturer, 9 of the 10 patients with whom they had contacted recently, were unaware that they had participated in a study, that they had undergone

randomisation, or that they had regularly attended scheduled clinic visits and evaluations[4]

KiTEC considered the sample size calculation to be unreliable and the methods used to describe it is not transparent and is not reproducible from the information provided in the paper. De Andres 2017 state that the outcome used to calculate sample size was "at least 50% pain relief" and they cite the previous studies which informed the expected treatment effect, a binary outcome, to be used in the calculation (Van Buyten 2013, Perruchoud 2013, Al-Kaisy 2014, Kapural 2015, North 1995, North 2005). However, De Andres 2017 also state that the difference to detect was "one point on the NRS scale between the groups", a continuous outcome. KiTEC re-calculated the sample size using the same data for proportion of patients achieving ≥50% pain reduction (76.5% in the intervention group and 47% in the control group) to detect a difference of 20% between the groups and found a statistical power of 80% would be achieved with 170 patients, 85 per group, calculated using the methods described in Noordzij 2010. KiTEC concluded that the study is underpowered to detect a statistically significant difference at the 5% level based on an outcome of at least 50% pain relief as quoted by the authors.

2.4. Was the HF10 therapy intervention implemented and used in an appropriate way?

Regarding the De Andres 2017 study, there are concerns over certain technical aspects of the device implantation and study procedure. There are also concerns that these issues have negatively affected the outcomes and blinding of the study.

The authors report that the alignment of the electrodes for the Senza and Medtronic devices were conducted in accordance with the respective manuals provided by the manufacturers. However, Figure 1.a does not depict the lead alignment they proposed for the Senza device (two electrode leads either side of the spinal cord, staggered to stimulate an area corresponding to vertebrae T8-T11). Instead this image depicts standard paraesthesia-based lead placement (as used in the comparator group)[5]. Figure 1.b and 1.c are schematics of staggered lead placement across T8-T11. If the leads were not placed correctly, this will have undoubtedly affected the clinical outcomes. KiTEC discussed the lead alignment in De Andres 2017 with a Consultant in pain medicine and neuromodulation and they had concerns that the area of stimulation used

[4] Based on information communicated by Nevro to NICE.
[5] This information was confirmed by Nevro to NICE.

was too diffuse to achieve effective pain reduction. They suggested that normal clinical practice is to focus the stimulation more precisely on vertebrae T9-T10. This is also reported in the Senza RCT where it is reported that lead position for HF10 therapy was based on extensive empirical observation that most patients respond to stimulation application near T9/T10, while allowing for patient variation by covering T8 to T11.

The programming of the Senza device also deviated from the manufacturer's recommendations. As reported by Nevro, on a number of occasions including within the first 12 months from implant programming. Computer records show that the follow-up clinical team or the implanting clinician requested that the patients be programmed with LF-SCS, paraesthesia-based programs or other non-standard configurations. It appears based on the information provided by the manufacturer's that the clinical team involved with the study deviated in some occasions from the recommended HF10 algorithm as reported in the SENZA-RCT. The manufacturer states that the treatment algorithm was not followed consistently. Clinic visits were irregular and 'as needed'. The manufacturer states that visit should have occurred at defined intervals of 1, 3, 6 and 12 months. Table 2 and Table 3 below present the studies technical characteristics for De Andres 2017 and Senza RCT. The basic technical aspects for frequency, pulse width and amplitude were similar between the De Andres 2017 and Senza RCT for both the intervention and the comparator.

Table 2: Studies technical characteristics intervention

	De Andres 2017	Senza RCT
Frequency	10000Hz	10000Hz
Pulse width	30 µsec	30 µsec
Amplitude (range)	1.5 – 5 mA	1.6 – 7.2 mA

Table 3: Studies technical characteristics comparator

	De Andres 2017	Senza RCT
Mean frequency	40 Hz	40 to 77Hz
Pulse width (range)	300 µs to 450 µs	346 µs to 591 µs
Amplitude (range)	4.5 mA to 8 mA	3.6 mA to 8.5 mA

2.5. Are all the primary and secondary outcomes adequately reported?

As previously stated although De Andres 2017 state that the outcome used to calculate sample size was “at least 50% pain relief” and they cite the previous studies which informed the expected treatment effect, a binary outcome, to be used in the calculation they then proceed to state that the difference to detect was “one point on the NRS scale between the groups”, a continuous outcome. Please see in addition our comments on sample size calculation and definition of the primary outcome as outlined in section 2.3.

Furthermore, the authors proceed to undertake multiple statistical comparisons presented in tables 3-6 without any adjustment for statistical significance and with an already limited sample size. They also proceed to undertake individual time point comparisons that are unnecessary and difficult to comprehend as reported in the respective tables. To this end all reported secondary outcomes results are considered unreliable.

2.6. Are the results consistent with other studies on spinal cord simulation?

Taylor 2014 presented their findings from an update SR and meta-analysis of LF-SCS of their previous SR in 2005 (Taylor 2005). Their original SR reported 62% (95% CI: 56% to 69%) achieving an equivalent of 50% or more pain relief following SCS at a mean follow-up of 26 months. The level of pain relief seen in the update review was consistent[6] with the their 2005 findings reporting mean level of pain relief for the comparator LF-SCS across studies of 53% (95% CI: 47% to 59%) at an average follow-up of 24 months (Taylor 2014) in studies using an objective definition such as ≥ 50% reduction in pain. On the contrary, De Andres 2017 reported a much lower reduction in pain with LF-SCS at 12 months follow-up of just 24%.

Despite the fact that both De Andres 2017 and Senza RCT used a ≥50% reduction in pain as a cut-off for proceeding from the trial phase to permanent implantation, in the De Andres study a modest 30-40% reduction in pain is reported for the intervention and the comparator indicating deviation from the findings of Taylor 2014 for both arms of the study. However, according with the authors in De Andres 2017, the primary purpose was to assess efficacy of HF10 in subjects who successfully completed the trial phase, therefore, only performing PP analysis and not ITT.

[6] This was based on the overlapping 95%CIs between the reported pooled values.

As a result, the 30-40% reduction reported by the authors from analysing only the sample of patients who successfully completed the trial phase cannot be justified when a selection criterion of ≥50% reduction in pain is applied leading to the conclusion that the patients were poorly selected for permanent implantation[7].

3. De Andres RCT

3.1. Was the trial fully or partially blinded? How could this have impacted the results?

The SR and meta-analysis by Taylor 2014 concluded that only 19% of the SCS studies reported a blinding design or independent assessment of the outcomes. Furthermore, due to the nature of the treatment, blinding of patients and investigators was not possible. Although evidence of comparative effectiveness is best provided by double-blind RCTs, it is not possible or ethical to conduct a blind trial of SCS because the technical goal of SCS treatment is to overlap the area of pain with perceptible paraesthesia (North 2005).

According to De Andres 2017 the evaluators who collected pain ratings and other outcome measures were blinded to the subjects' group allocations throughout the process. The authors also claim that the patients were also blinded and advised that both treatments were equally effective and that they may experience paraesthesia as part of their treatment. Although the evaluators who collected pain ratings were blinded in De Andres 2017 it is not possible to blind the patients as experiencing paraesthesia is a characteristic of only LF SCS. For example the authors clearly state that in the LF-SCS, stimulation patterns were tested for optimal overlap between paraesthesia and the region of the subject's back and leg pain by adjusting the position of the electrodes until paraesthesia was identified and covering the entire area of pain, however, this step was skipped in the HF10. Furthermore, these patients are given a remote control and a manual with instructions about the device which will make the intervention identifiable to the user in the first instance. The authors do not provide any information on steps taken to ensure adequate blinding by making the two devices hardware and instructions for use indistinguishable. Finally, several of the Senza HF10 hardware components used by the patients display the characteristic 'Nevro' logo (Senza HF10 IFU) that makes the intervention distinguishable (Figure 1, Figure 2).

[7] According with KiTEC's clinical experts' views in clinical practice a much higher threshold than ≥50% reduction in pain is used as a criterion for permanent implantation.

Figure 1: Patient remote control unit provided to patients during the trial phase clearly features the device's trademark 'Nevro' that will make it distinguishable from any other SCS device.

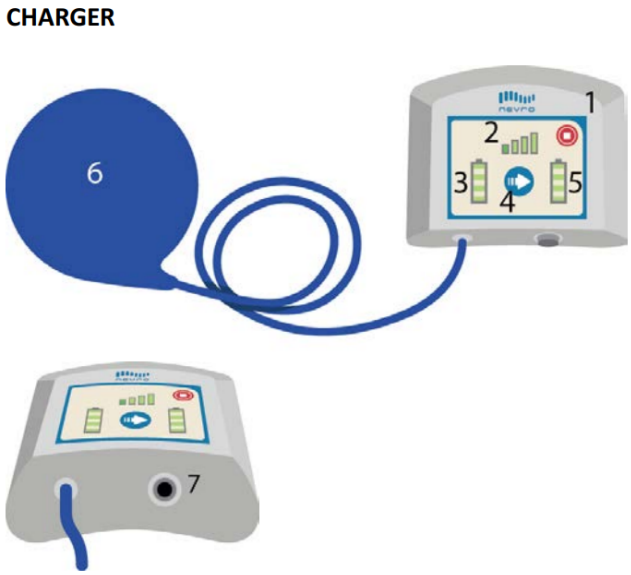

Figure 2: Device charger to recharge the implantable pulse generator featuring the device's trademark.

Given that the primary outcome (pain reduction) is a patient reported outcome, the pragmatic inability to blind the participants (despite claims from the authors for the opposite) questions the methodological superiority of De Andres 2017 vs. the Senza RCT.

3.2. Should this evidence be legitimately considered or not by the committee?

As outlined in detail in the above sections, the De Andres RCT credibility as a well planned and executed prospective RCT is severely questioned. As a result KiTEC recommends that the committee should not consider the authors results with regards to the decision for adoption of the Senza HF10 SCS.

4. SENZA RCT

4.1. Could patients be influenced by marketing material?

The effect of SCS seems to be constant in all trials and therefore not depended on the total follow-up time with the exception of an original decrease from baseline on the first follow-up assessment. Whether this is attributed to a placebo effect or to adjustment of the pain medication immediately after the surgical implantation is not known. In De Andres 2017, an average reduction of 30–40% with respect to the initial value at first follow-up was noted. This response was reduced to a 20–25% reduction with respect to the baseline value at 12 months. Both De Andres 2017 and Senza RCT lack a sham control group that would help distinguish the magnitude of the placebo effect. Previously, a sham-controlled SCS trial showed no difference between 5kH-SCS and sham or LF-SCS stimulation (Perruchoud 2012). However, the major limitations of that study included the enrolment of implanted patients already exposed to long-term conventional SCS treatment, the use of 5kHZ rather than 10kHz, and failure to apply stimulation at the vertebral level where HF10 is known to be maximally effective (T9-T10). Because of the possibility of a placebo effect, in addition to any possible specific therapeutic mechanisms, it cannot be excluded that a portion of the SCS therapeutic effect observed in all trials is delivered via placebo mechanisms (Al-Kaisy 2018). In the Al-Kaisy 2018 cross-over RCT for example, sham treatment demonstrated an approximate 3-point VAS change from baseline resulting in similar analgesic effects to 1200Hz and 3030 Hz SCS (Al-Kaisy 2018).
Because of the possibility of a placebo effect long-term follow-up is essential to distinguish between true effect attributed to the intervention and placebo effect. To this end the Senza RCT that showed a sustained effect over 2 years follow-up has the advantage over De Andres 2017. Based on the above it is unlikely that the stable effect of HF10 over 2 years observed in Senza RCT could be attributed to placebo due to marketing material.

4.2. Was there potential bias introduced by the funding of the study?

The majority of studies in the field of SCS is based on evidence produced from studies funded by the manufacturer of the technologies. Table 4 below reports RCTs with LF-SCS included in TA159 and their funding sources. Measures that reduce the possibility of introducing bias due to funding obtained by the device manufacturer include (North 2010):

- a strict randomisation procedure
- the use of an impartial third party to collect data
- the use of an independent group of statisticians to analyse data
- the execution of the study in a multicentre settings by multiple clinicians

The SENZA-RCT was conducted in a multicentre setting, with a degree of oversight by the FDA and an independent data and safety monitoring board, and implemented a strict randomisation process. As a result, although potential bias introduced by the funding of the study by the manufacturer cannot completely be eliminated as industry-funded studies are more likely than others to produce results favourable to the intervention the above parameters minimise the potential bias to the study results.

Table 4: Examples of RCTs in LF-SCS and their respective funding sources.

Study name	Intervention	Funding source
PROCESS	Synergy™ system, Medtronic, Inc., Minneapolis, MN	Medtronic
EVIDENCE	Boston Scientific Corporation, Valencia, CA, USA	Boston Scientific

4.3. Were there any other forms of bias? If yes, how did this impact the results?

The SENZA-RCT was powered according to the primary objective of demonstrating non-inferiority, if non-inferiority was demonstrated, superiority could then be assessed secondarily (Kapural 2015). This is becoming increasingly common in RCT trials and there are no concerns raised with regards to the power calculations reported in the SENZA RCT.

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6. Appendix 1

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Medical technology guidance

Clinical effectiveness evidence review
Senza for delivering high frequency spinal cord stimulation to treat chronic neuropathic pain

Objectives:
To assess the evidence for the clinical effectiveness of Senza which aligns with the published NICE scope

Background:
NICE started developing medical technologies guidance on Senza in May 2017. The topic has followed a standard guidance development process with a committee meeting in September 2017, followed by a public consultation. Some further relevant recently published evidence was identified during the consultation including another RCT (De Andres et al.). At the following committee meeting in December 2017 the committee decided to change the draft recommendations because of the uncertainty in patient benefit and cost-savings following the comments in the consultation and the additional evidence. A second consultation was held and comments from this raised uncertainties about the validity of the De Andres study. A letter from the editors was published in the journal addressing some of the issues. The N&Y team are contacting the journal to establish if there is any further ongoing action or correspondence about the paper.

The next committee meeting is scheduled for June 22 2018.

Considerations:

- Please do this review as independently as possible with as little reference as possible to the work of the previous EAC
- The evidence has already been identified from literature searches and so the review should focus on the studies listed below.
- This review should be conducted independently from the original assessment. The comments from both consultations have included a range of polarized and contradictory opinions about the evidence base. The committee chair considers an independent HTA view of the evidence might help inform the committee decision-making.
- The Kitec team should contact the MTEP team if they have any specific queries for a clinical expert adviser or for the company. The Kitec team should contact its own experts to determine if the HF10 therapy was correctly implements in the trials.
- The review should focus on looking at the reliability and robustness of the RCT evidence because we have received polarised views from consultees about these studies in the

consultation. Some key issues identified which should be addressed within the review include:

General review:

a) Was the trial conducted according to European clinical trial standards with respect to ethical and regulatory considerations?
b) Is the patient population clearly described and is it consistent with the patient population described in the decision problem?
c) Was the trial planned as a prospective randomised trial? Was it adequately powered?
d) Was the HF10 therapy intervention implemented and used in an appropriate way?
e) Are all the primary and secondary outcomes adequately reported?
f) Are the results consistent with other studies on spinal cord simulation

De Andres RCT

a) Was the trial fully or partially blinded? How could this have impacted the results?
b) Should this evidence be legitimately considered or not by the committee?

Senza RCT

a) Was there potential bias introduced by the funding of the study?
b) Could patients be influenced by marketing material?
c) Were there any other forms of bias? If yes, how did this impact the results?

- A briefing meeting will be arranged for early in week commencing 11th June so the MTEP team can answer any queries.

Output:

A brief report containing a review of the evidence and the EAC's conclusions about the clinical effectiveness of Senza. The EAC should be clear about the weight they have attached to the different RCTs to reach this conclusion and if the de Andres should not be considered by the committee the reasons for its exclusion. This must be delivered to NICE on the 20 June at the latest for circulation to the committee.

Sources of information:

The relevant evidence is as follows:

1. Al-Kaisy A, Van Buyten J P, Smet I, Palmisani S, Pang D and Smith T 2014 Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study Pain medicine (Malden, Mass.) 15 347-54
2. Al-Kaisy A, Palmisani S, Smith T E, Pang D, Lam K, Burgoyne W, Houghton R, Hudson E and Lucas J 2017a 10 kHz High-Frequency Spinal Cord Stimulation for Chronic Axial Low Back Pain in Patients With No History of Spinal Surgery: A Preliminary, Prospective, Open Label and Proof-of-Concept Study Neuromodulation 20 63-70
3. Al-Kaisy, A., Palmisani, S., Smith, T.E., Carganillo, R., Houghton, R., Pang, D., Burgoyne, W., Lam, K. and Lucas, J., 2017b. Long-Term Improvements in Chronic Axial Low Back Pain Patients Without Previous Spinal Surgery: A Cohort Analysis of 10-kHz High-Frequency Spinal Cord Stimulation over 36 Months. Pain Medicine.

4. Amirdelfan, K., Yu, C., Doust, M.W., Gliner, B.E., Morgan, D.M., Kapural, L., Vallejo, R., Sitzman, B.T., Yearwood, T.L., Bundschu, R. and Yang, T., 2018. Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT. Quality of Life Research, pp.1-10.
5. De Andres, J., Monsalve-Dolz, V., Fabregat-Cid, G., Villanueva-Perez, V., Harutyunyan, A., Asensio-Samper, J.M. and Sanchis-Lopez, N., 2017. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Medicine, 18(12), pp.2401-2421.
6. Kapural L, Yu C, Doust M W, Gliner B E, Vallejo R, Sitzman B T, Amirdelfan K, Morgan D M, Yearwood T L, Bundschu R, Yang T, Benyamin R and Burgher A H 2016 Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial Neurosurgery 79 667-77
7. North, R, Eldabe 2018, S; Neuromodulation Device Comparison Studies: Coming of Age Revisited, Pain Medicine, , pny064, https://doi.org/10.1093/pm/pny064
8. Rapcan R, Mlaka J, Venglarcik M, Vinklerova V, Gajdos M and Illes R 2015 High-frequency - Spinal Cord Stimulation Bratisl Lek Listy 116 354-6
9. Russo M, Verrills P, Mitchell B, Salmon J, Barnard A and Santarelli D 2016 High Frequency Spinal Cord Stimulation at 10 kHz for the Treatment of Chronic Pain: 6-Month Australian Clinical Experience Pain Physician 19 267-80
10. Tiede J, Brown L, Gekht G, Vallejo R, Yearwood T and Morgan D 2013 Novel spinal cord stimulation parameters in patients with predominant back pain Neuromodulation 16 370-5
11. Van Buyten, V., Wille, F., Smet, I., Wensing, C., Breel, J., Karst, E., Devos, M., Pöggel-Krämer, K. and Vesper, J., 2017. Therapy-Related Explants After Spinal Cord Stimulation: Results of an International Retrospective Chart Review Study. Neuromodulation: Technology at the Neural Interface, 20(7), pp.642-649.

Key documents from the evaluation are available on the NICE website and include the scope, the company submission, the assessment report, EAC advisory document on additional evidence.