Drug costs used in economic model of Senza HF10 therapy (MT330)

The issue

In the *de novo* economic model to support the cost saving potential of Senza HF10 spinal cord stimulation (SCS) compared with traditional non-rechargeable SCS (TNR-SCS) or traditional rechargeable SCS (TR-SCS), the authors used inflated costs from the study by Taylor et al. (2010) [1] which in turn was based on inflated values from the model used in TA159 [2]. The EAC made a critique that it was inappropriate to inflate drug prices as they are subject to a wide range of other non-inflationary factors such as:

- Price fluctuations due to introduction of comparator drugs.
- Move from proprietary to generic products (e.g. recent introduction of generic pregabalin).
- Changes in management strategies (e.g. use of proton pump inhibitors [PPIs] combined with non-steroidal anti-inflammatory drugs [NSAIDS])

It is likely that in the absence of a new proprietary drug class to treat pain then the overall drug management costs will be subject to downward pressures. Another important issue is that patients with neuropathic pain represent a heterogeneous population with different medication needs. There is no such thing as an "average" patient.

The original values for drug prices cited in TA159 were calculated from data from the PROCESS trial [3]. This study reported proportions of people taking drug classes, but did not report on the further granularity of individual drug types prescribed. For this reason, as well as changes to drug pain management in recent years, the EAC believes re-assessing the cost of drug management using bottom-up micro-costing would not be a trivial undertaking.

Sensitivity analysis

The company undertook univariate sensitivity and found that under two scenarios adjusting the drug costs would result in Senza HF10 being cost incurring (Table 4.6 of Assessment Report). These were by assuming drug costs associated with SCS were £8,412 (upper limit of 95% CI) rather than £2,012 used in the bases case, and by assuming the drug costs of conventional medical therapy (CMM) alone were £0 (lower limit of 95% CI) rather than £3,167 used in the base case. Although superficially this suggests that the model is sensitive to drug costs, the EAC considers that this is misleading. This was because univariate sensitivity analysis was used, whereupon the cost of drugs in SCS or CMM were altered independently, rather than in combination. As a result of this:

- In the first scenario, it was assumed drug costs associated with SCS were more than double that of CMM alone. This is not plausible as it would contradict all the empirical evidence (and common sense) that shows use of SCS is associated with reduced drug use. For instance, the PROCESS trial reported a downward trend in analgesic use in the SCS arm compared with the CMM arm [3].
- In the second scenario, a zero cost of drug management is attached to CMM whereas drug treatment of patients receiving SCS is unchanged from baseline (£2,012). Again, this is simply not plausible.

Additional sensitivity analysis

The univariate sensitivity analysis used to alter drug costs in the model was inappropriate because it assumed drug costs in patients receiving SCS or CMM were independent, when they are clearly not (that is, a reduction, or increase, in drug costs will affect both cohorts approximately proportionately). The EAC has therefore investigated four further hypothetical scenarios to assess their impact on the cost-saving potential of Senza-RCT (Table 1). These are:

- *Scenario 1*: Drug costs are equal in both groups. This is an extremely conservative scenario not supported by empirical evidence.
- *Scenario 2*: Drug prices are reduced by 50% in both SCS and CMM cohorts.
- *Scenario 3*: Drug prices are reduced by 50% in patients receiving CMM only. This is a very unlikely scenario as both cohorts would be expected to report proportionate drug cost reductions.
- *Scenario 4*: Drug prices are increased by 50% in both SCS and CMM cohorts.

Table 1. *Scenario analysis of changes to drug costs.*

Scenario	Incremental cost saving with HF10 compared with TNR-SCS	Incremental cost saving with HF10 compared with TR-SCS
1	£4882	£1922
2	£6345	£3385
3	£3816	£856
4	£10,576	£7616

Thus as can be seen, in all these scenarios Senza-HF10 remains cost-saving.

Conclusion

In the opinion of the EAC, estimating the cost of drug management in the relevant patient cohorts would not be a trivial undertaking. Furthermore, it is difficult to foresee any alternative values of drug costs for CMM and SCS patients which would change the direction of results (i.e. report Senza HF10 is cost-incurring). The EAC would also like to draw attention to the results of the probabilistic sensitivity analysis (PSA) performed in the model. This analysis randomly varied the costs of drug management (over the 95% CI range) with 10,000 iterations (as well as other parameters). It showed there was approximately 75% chance that Senza HF10 was cost-saving.

References

1. Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. The Clinical journal of pain. 2010 Jul-Aug;26(6):463-9.
2. Simpson EL, Duenas A, Holmes MW, Papaioannou D. 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); 2008.
3. 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.

Medicines and Technologies Programme
Adoption Scoping Report GID-MT515
Senza Spinal Cord Stimulation (SCS) System for the treatment of chronic pain

SUMMARY – for MTAC1 meeting

Adoption Levers

- Relative ease of insertion, reduced procedure time
- Patient preference
- Price parity with other SCS devices

Adoption Barriers

- Clinical confidence in new device
- Access to funding for any SCS procedure

1. Introduction

The Adoption team has collated information from healthcare professionals working within NHS organisations some of whom have experience of using the Senza Spinal Cord Stimulation (SCS) System.

This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use.

2. Contributors

The Adoption team spoke to 3 NHS clinicians, a consultant neurosurgeon, a consultant in pain medicine and anaesthesia and a professor of pain management and rehabilitation.

The consultant neurosurgeon estimates that he has implanted in excess of 1,000 SCS devices in his 29 years of practice and between 108 and 144 Senza SCS devices in the past 3 years (3-4 per month).

The consultant in pain medicine and anaesthesia estimates she has implanted 550 SCS devices in the past 10 years and approximately 96 Senza SCS devices in the past 4 years (2 per month). The specialised pain centre this consultant works in is actively involved in SCS research so a large number of patients are on trials with other devices.

3. Existing NICE guidance on SCS

The guidance[1] published in 2008 recommends spinal cord stimulation (SCS) 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 specified assessment.

The guidance gives examples of 2 neuropathic conditions: failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) but is not limited to these.

The recommendations in TA159 would also apply to the Senza SCS system, i.e. non-surgical refractory chronic back pain (with or without leg pain) who are not candidates for spinal surgery if the pain is of neuropathic origin and fits the criteria above.

If the indication is to cover pain that is not of neuropathic origin, TA159 does not apply.

Guidance review 2013

The guidance was considered for review in November 2013[2]. References from October 2007 onwards were reviewed and as a result it was considered that the new evidence supported the existing recommendations and that the guidance should be placed on the static list until such time that further evidence is available. It was noted that an additional SCS device manufacturer had received CE marking but that this did not impact the guidance because individual devices are not specified in the recommendations of TA159. The review noted that there were several studies investigating the cost effectiveness of spinal cord stimulation in people with neuropathic pain, whether spinal cord stimulation should be considered earlier than last resort treatment, the impact of psychological factors on spinal cord stimulation outcomes and whether high frequency or standard frequency spinal cord stimulation should be used. It was concluded that none of the results would change the current recommendation in TA159 for neuropathic pain.

During consultation the Neuromodulation Society of the UK and Ireland pointed out that an additional 3 new companies had achieved a CE mark (including Nevro) and

[1] https://www.nice.org.uk/guidance/ta159

[2] https://www.nice.org.uk/guidance/TA159/documents/appendix-b-proposal-paper-presented-to-the-institutes-guidance-executive-2

that a study on the analgesic efficacy of high frequency spinal cord stimulation had already published[3]. These comments were noted.

The review decision in February 2014[4] was that TA159 would be transferred to the static list of technology appraisals. The guide to the process of technology appraisal[5] states that if guidance is designated as static guidance, then NICE considers whether a review is required 5 years after the guidance is added to the static list. This is called a static list review. NICE does a literature search to see if there is any new evidence to update the existing recommendations. If it is decided that the evidence base has changed significantly, then a full review proposal is developed to assess whether an update of the guidance is required.

4. Care pathway

The British Pain Society's consensus document on spinal cord stimulation for the management of pain: recommendations for best clinical practice[6] published in 2009. The statement concluded that there is clinical evidence from randomised controlled trials to support use of SCS in pain from failed back surgical syndrome (FBSS), complex regional pain syndrome (CRPS), neuropathic pain, and ischaemic pain and concurs with NICE that further high-quality research on the use of SCS in chronic pain of ischaemic origin is required.

Neuropathic pain in adults: pharmacological management in non-specialist settings[7] (CG173) updated in December 2104 states that all neuropathic pain (except trigeminal neuralgia) should be treated with anticonvulsants before any other treatment modality is considered.

NICE guidance on low back pain and sciatica[8] (published November 2016) does not include recommendations on SCS. The responses to comments[9] received during consultation on the scope of the guideline, suggesting that SCS has a role in the management of chronic pain in the absence of surgical options, state that this is covered by TA159 and will be cross-referred to in the guideline.

Does the Senza system involve any change to the care pathway?

Contributors report that there is no change to the care pathway in that they have been implanting the Senza SCS system on a 'trial' basis for 1 – 2 weeks and if they achieve more than 50% reduction in pain score proceeding to a permanent implant.

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[3] http://www.ncbi.nlm.nih.gov/pubmed/23425338
[4] https://www.nice.org.uk/guidance/TA159/documents/review-decision-february-2014
[5] https://www.nice.org.uk/article/pmg19/chapter/6-Reviews
[6] https://www.britishpainsociety.org/static/uploads/resources/files/book_scs_main_1.pdf
[7] Neuropathic pain in adults: pharmacological management in non-specialist settings
[8] https://www.nice.org.uk/guidance/ng59
[9] https://www.nice.org.uk/guidance/GID-CGWAVE0681/documents/low-back-pain-and-sciatica-scope-consultation-comments-table-2

The conversion rate for low frequency SCS has been approximately 80%, however they are currently achieving a near 100% conversion rate with the Senza SCS system and are now considering whether a trial phase is necessary, however as current NICE guidance (TA159) stipulates a trial phase they are continuing with this.

As with all SCS device insertions a company representative attends to ensure correct device placement and to programme the device for impedance.

5. Commissioning

Trauma[10] is one of six NHS England National Programmes of Care (NPoC) overseeing the commissioning of specialised and highly specialised services. It consists of 7 Clinical Reference Groups (CRGs). These provide clinical advice and leadership on the specialised services in the Trauma NPoC. These groups of clinicians, commissioners, public health experts, patients and carers use their specific knowledge and expertise to advise NHS England on the best ways that specialised services should be provided. The Specialised Pain CRG[11] covers services within a specialised pain centre and has developed a service specification[12] which clearly defines the standards of care expected from organisations funded by NHS England to provide specialised services for pain management in adults. This includes the use of spinal cord stimulation in these centres.

There is not currently a national specification for pain services outside of these specialist centres and not every Clinical Commissioning Group (CCG) commissions this activity explicitly from their local provider(s). A Freedom of Information request was sent to all CCGs asking for the number of spinal cord stimulator patients each CCG funded in 2013-14. An online search reveals that many responded stating that spinal cord stimulation is a specialised service commissioned by NHS England and therefore not routinely funded by CCGs. This is not entirely accurate as only spinal cord stimulation performed in a specialist centre is commissioned by NHS England. Any SCS device insertion performed outside a specialist centre needs to be commissioned at CCG level.

Those CCGs that have published their individual commissioning policies for spinal cord stimulation on line often stipulate that an Individual Funding Request (IFR) must be made and patients must meet the specified criteria of TA159. Contributors to this resource confirmed that this is standard for SCS. A number of CCGs have also included SCS in their list of procedures of limited clinical effectiveness:

- a procedure where the clinical effectiveness of that procedure is either absent or evidence shows weak efficacy and long term benefits reached

[10] https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/
[11] https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d07/
[12] https://www.england.nhs.uk/wp-content/uploads/2013/06/d08-spec-serv-pain-mgt.pdf

- ***a procedure which is clinically effective but only under certain conditions, such as when a person meets certain criteria, otherwise more conservative alternatives should be tried first***

- a treatment of a condition where not funding the treatment will not result in a significantly adverse effect on the patient's physical or mental health

These are procedures not routinely funded or requiring prior funding approval.

Both contributors to this resource who implant SCS devices are employed within an NHS England commissioned specialised pain centre. They report that colleagues from other hospitals with the skills, competencies and experience in SCS implants will refer to the specialist pain centre rather than apply for an IFR.

6. Resource impact

6.1. Procurement

The Senza SCS system is on the NHS Supply Chain. Several high cost drugs, devices and listed procedures are not reimbursed through national prices. Since April 2016 these high cost devices[13] have been covered by a single national approach for purchasing and supplying (agreed between NHS England and NHS Business Services Authority). The system for hospital trusts to order devices for specialist services is operated by NHS Supply Chain[14]. The approach involves a transactional model involving zero cost to healthcare providers.

Rather than separate hospital trusts paying for the devices and being reimbursed by NHS England as previously happened, providers place orders for devices with NHS Supply Chain at zero cost to them. NHS Supply Chain will then place the order with suppliers and invoice NHS England.

The new system covers all 'high-cost tariff excluded devices' set out in the List of High Cost Devices in the 2017/18 and 2018/19 NHS National Tariff Payment System (Annex A)[15]. These are devices that are expensive and are paid for on top of the national price, or tariff, for the procedure in which they are used. This is because the devices are provided by a relatively small number of centres, and it is recognised that the costs would not be fairly reimbursed if they were simply funded through the tariff.

Deep brain, vagal, sacral, spinal cord and occipital nerve stimulators are all included in this list for 2017/19.

[13] https://www.england.nhs.uk/commissioning/spec-services/key-docs/medical-devices/
[14] https://www.supplychain.nhs.uk/news/company/centralisation-of-the-supply-chain-for-high-cost-tariff-excluded-devices/
[15] https://improvement.nhs.uk/resources/national-tariff-1719/#h2-tariff-documents

6.2. Tariff

The 2017/18 national tariff[16] for HRG AA60A (Insertion of Neurostimulator for Treatment of Neurological Conditions, 19 years and over) is £2,516 while the tariff for HRG AA60B (Insertion of Neurostimulator for Treatment of Neurological Conditions, 18 years and under) is £3,020.

This assumes the procedure is classed as one of the following OPCS codes and also requires a primary diagnosis of pain:

OPCS Description

A48.3 Insertion of neurostimulator adjacent to spinal cord

A70.1 Implantation of neurostimulator into peripheral nerve

A48.7 Insertion of neurostimulator electrodes into the spinal cord

Any high cost devices will be paid for separately in addition to the HRG tariff by the commissioner as an excluded device as discussed above.

A costing template[17] was produced to support the adoption of TA159. This can be adapted to suit local circumstances and updated to reflect current tariff levels. These costs factored in trial stimulation and estimated 80% of trials would result in a permanent implant.

6.3. Choice of device

In section 4.3 of TA159 (consideration of the evidence) the guidance committee was aware that there was a range of SCS devices available and concluded that if, after consultation between the responsible clinician and the patient, it was considered that more than one SCS system was likely to be equally appropriate, the least costly should be used. The committee considered that assessment of cost should take into account acquisition costs, the anticipated longevity of the system, the stimulation requirements of the person with chronic pain and the support package offered.

7. Training

The British Pain Society best clinical practice recommendations state that clinicians performing the SCS interventions must understand the multidisciplinary management of pain. They must have and maintain relevant surgical competence in insertion of the SCS system and management of complications such as infection. This will usually be a consultant in pain medicine, neurosurgeon, or spinal surgeon. The multidisciplinary pain management team must have access to a spinal surgeon or neurosurgeon competent to deal with the complications of SCS.

[16] https://improvement.nhs.uk/resources/national-tariff-1719/#h2-tariff-documents
[17] https://www.nice.org.uk/guidance/ta159/resources

7.1. Will any clinician already performing SCS be able to implant the Senza SCS system?

Clinicians with experience of implanting the Senza SCS system report that the procedure to implant it is technically more straightforward than for traditional low frequency SCS as it is not topographically dependant and paraesthesia mapping is not required. This can significantly reduce the time required for the procedure.

The consultant neurosurgeon reported an average procedure time for implantation of 20 minutes for the Senza SCS system compared with 20 – 90 minutes for low frequency SCS (dependant on accuracy of placement).

The consultant in pain medicine and anaesthesia stated that her quickest SCS insertion had been 12 minutes for a temporary trial, leading up to an hour for a more difficult insertion. The use of the Senza SCS system can increase capacity to insert 3 devices with temporary trials in a theatre session as opposed to 2 low frequency devices. In the case of permanent trials the procedure may not be speeded up.

Clinicians contributing to this scope estimate that over 95% of SCS procedures are performed by neurosurgeons or anaesthetists.

7.2. Is any additional training required?

Both clinicians with experience of implanting the Senza SCS system and low frequency SCS report that no additional training is needed and other than there being no requirement for paraesthesia mapping, all elements of the procedure are the same.

7.3. Is the Senza SCS system any more likely to result in complications?

Neither clinician currently implanting the Senza SCS system report any change in complication rates between this system and low frequency SCS systems.

8. Patient selection and acceptance

Patient acceptance has not been highlighted as an adoption issue particularly as the device does not induce the paraesthesia of low frequency SCS devices and previous research has shown positive outcomes.

Another advantage identified has been the ability to drive and operate machinery whilst the device is switched on.

The consultant neurosurgeon reports that they have implanted the Senza SCS system into patients who would not have been assessed as suitable for low frequency SCS. In particular, people with more widespread pain from failed back surgery, and have had good results.

The consultant neurosurgeon reported a case where a patient with brachial plexus lesions who had a low frequency SCS device implanted 15 years ago was offered and agreed to implantation of the Senza SCS device to see if a greater reduction in

pain score could be achieved. Post operatively this patient has reported improved satisfaction with the high frequency device.

The consultant neurosurgeon also reported that their team had conducted a small trial whereby 12 consecutive patients had the frequency of the Senza SCS system changed from high to low frequency part way through their trial period. All patients requested the permanent implant to be on high frequency.

The consultant in pain medicine and anaesthesia reported that some people prefer not to experience paraesthesia but there are some patients who still opt for low frequency as the sensation they perceive reassures them that the device is working.

This consultant reported that the results for FBSS have been excellent using the Senza SCS system for low back and leg pain.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme (MTEP)

Sponsor submission of evidence: MT515

Evaluation title: SENZA™ spinal cord stimulation for the treatment of chronic pain

Sponsor: Nevro Corporation

Date sections A and B submitted: 7th June 2017

Date section C submitted: 5th July 2017

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Abbreviations

AE(s)	Adverse event(s)
CA	California
CASP	Critical appraisal skills programme
CE	Conformité Européenne
CG	Clinical Guideline
CGIC	Clinician global impression of change
CI	Confidence interval
CMM	Conventional medical management
CRPS	Complex regional pain syndrome
EQ-5D	EuroQoL-5 dimension
FBSS	Failed back surgery syndrome
GAF	Global assessment of functioning
HRQoL	Health-related quality of life
Hz	Hertz
ICER	Incremental cost-effectiveness ratio
IPG	Interventional Procedure Guidance
ITT	Intention-to-treat
MRI	Magnetic resonance imaging
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPRS	Numerical pain rating scale
NRS	Numerical rating scale
N/R	Not reported
ODI	Oswestry disability index
PGIC	Patient global impression of change
PNFS	Peripheral nerve field stimulation
PSS	Personal social services
QALY(s)	Quality adjusted life year(s)
RCT(s)	Randomised controlled trial(s)
SAE(s)	Serious adverse event(s)
SCS	Spinal cord stimulation
SD	Standard deviation

SE	Standard error
SF-36	Short form-36
TAG	Technology Appraisal Guidance
TNR-SCS	Traditional non rechargeable low-frequency spinal cord stimulation
TR-SCS	Traditional rechargeable low-frequency spinal cord stimulation
TTO	Time trade-off
USA	United States of America
UK	United Kingdom
VAS	Visual analogue scale

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

The decision problem is summarised in Table 1 along with rationale for variation from the scope as necessary.

Table 1: Statement of the decision problem

Key parameter	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Patients undergoing spinal cord stimulation for chronic pain in line with NICE Technology Appraisal 159	None	N/A
Intervention	HF10™ therapy using the Senza™ spinal cord simulation system	None	N/A
Comparator(s)	Low frequency spinal cord stimulation (up to 1200 Hz)	None	N/A
Outcomes	• Pain scores (for example VAS score)	None	N/A
	• Duration of pain relief	None	N/A
	• Patient satisfaction relating for example to frequency of battery recharging	None	N/A
	• Health-related quality-of-life	None	N/A
	• Functional disability measures e.g. disability Index Score, Oswestry Disability Index and functional improvement including ability to drive and perform work-related activities	None	N/A
	• Opioid and other analgesic use	None	N/A
	• Device-related adverse events	None	N/A
	• Implantation time in theatre	Not included	Paraesthesia mapping is not required with HF10™ therapy. As a result, the surgical procedure is more predictable than traditional low-frequency SCS. This outcome has not been the subject of a study and therefore data are not available to include in this submission.

	• Incidence of paraesthesia	None	N/A
	• Implant lifetime	None	N/A
	• Reason for implant removal	None	N/A
	• Follow up appointments including attendance at pain clinics	Not included	The superior long-term outcomes of HF10™ therapy (see section B) versus traditional low-frequency SCS, could potentially reduce follow-up attendances at pain clinics allowing for more efficient service configuration. This outcome has not been the subject of a study and therefore data are not available to include in this submission.
	• Staff conducting device programming	Not included	Device programming for HF10™ therapy is likely to be quicker than traditional low-frequency SCS systems, as it is standardised to a limited number of optimised settings for each individual patient. As a result, HF10™ therapy is delivered using the same therapeutic algorithm irrespective of the skill or experience of the person responsible for device programming, allowing it to be performed by non-technical staff, e.g. a nurse. This outcome has not been the subject of a study and therefore data are not available to

			include in this submission. It would be valuable for NICE to seek expert opinion on the differences in time and staff requirements for device programming for HF10™ therapy versus traditional low-frequency SCS systems.
Cost analysis	Comparator(s): • Low frequency spinal cord stimulation (up to 1200 Hz) Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. This will include the trial and permanent implantation phases of the care pathway. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.	None	N/A
Subgroups to be considered	• Previous back surgery / failed back surgery syndrome	Not included	Interaction analysis from the SENZA-RCT demonstrates that the difference in pain relief for patients with previous back surgery / failed back surgery syndrome versus patients without previous back surgery is not statistically significant. Therefore, results of the economic analysis would probably not be impacted.

	• Chronic pain involving the limbs	Not included	Results from the SENZA-RCT (see section 7.6.1), demonstrate that HF10™ therapy works just as well for chronic pain of the limbs as it does for chronic pain of the back. At 24 months, HF10™ therapy provided a statistically significant mean difference in VAS pain score from baseline versus traditional low-frequency SCS for both back and leg pain. Therefore, results of the economic analysis would probably not be impacted.
	• Chronic pain involving the back	Not included	
	• Complex regional pain syndrome	Not included	The SENZA-RCT did not include complex regional pain syndrome patients. Therefore, data are not available to include in this submission.
Special considerations, including issues related to equality	People likely to benefit from this technology may have disabilities causing issues with mobility. They may be considered to be disabled if their condition has a substantial and long-term negative effect on the ability to do normal daily activities. Disability is a protected characteristic under the Act.	None	N/A

Abbreviations: Hz, hertz; N/A, not applicable; VAS, visual analogue scale.

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Brand name: Nevro® Senza™ Spinal Cord Stimulation System delivering HF10™ Therapy.

Approved name: Nevro® Senza™ Spinal Cord Stimulation System[a].

2.2 What is the principal mechanism of action of the technology?

Spinal cord stimulation (SCS) systems provide electrical stimulation (pulses) to the spinal cord to reduce pain perception. Electrical stimulation is delivered by small electrodes, which are placed via leads in the epidural space in the spinal cord near the region that supplies nerves to the painful area, and are connected to a compact, battery-powered neurostimulator implanted under the skin. Although the exact mechanism for pain control from SCS is not entirely understood, it is believed to result from direct or facilitated inhibition of pain transmission (1).

Traditional low-frequency SCS systems

Traditional SCS systems deliver low-frequency (40-60 Hz) electrical stimulation to the spinal cord to induce paraesthesia, a 'tingling' or 'buzzing' sensation to mask the patient's pain. An intra-operative step known as 'paraesthesia mapping' is required, during trial stimulation and when permanently implanting traditional low-frequency SCS systems. Paraesthesia mapping involves waking the patient in the operating theatre to ensure that the location of the leads and stimulation parameters produce paraesthesia which covers the patient's pain areas. When the SCS system is active, paraesthesia is always present and can be unpleasant: many patients find this a disturbing side effect of traditional low-frequency SCS systems. In addition, paraesthesia can sometimes cause a shocking or jolting sensation with changes in posture. For this reason, driving a vehicle or operating heavy machinery are contraindicated with traditional low-frequency SCS systems.

Senza™ SCS system delivering HF10™ therapy

In contrast, the Senza™ SCS system is **the only SCS system that delivers paraesthesia-free** HF10™ therapy. HF10™ therapy is the description of the unique, patented high-frequency (10,000 Hz), short-duration and low-amplitude waveform delivering electrical stimulation to the spinal cord.

With HF10™ therapy paraesthesia mapping is not required. The leads are placed in a consistent fashion in the vertebra (Figure 1), whilst the patient remains sedated. The first electrode of one lead is usually placed at the top of the T8 vertebra and the last electrode of the second lead placed at the bottom of the T11 vertebra with some overlap of the leads at T9/T10). Therefore, with HF10™ therapy surgical procedure time is likely to be shorter and its duration more predictable than traditional low-frequency SCS. In addition, the experience is less onerous for patients with HF10™ therapy.

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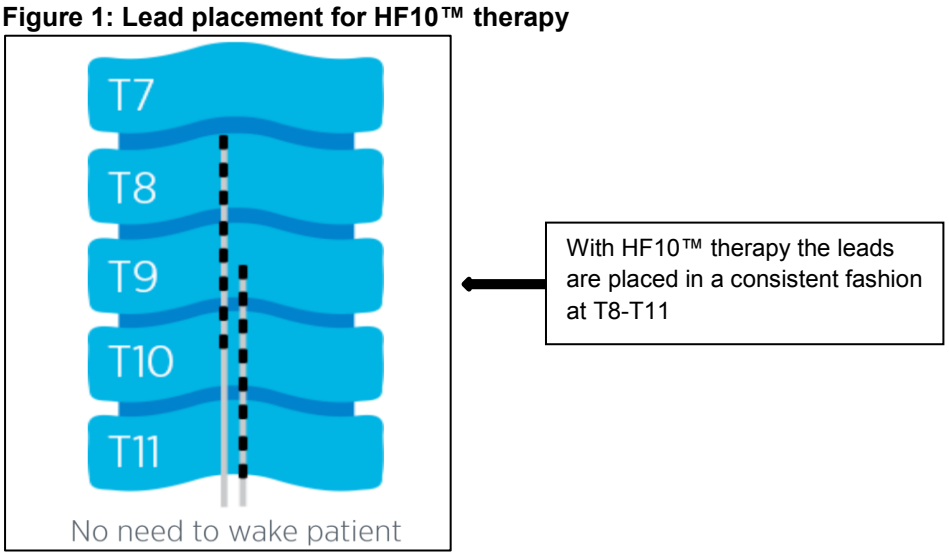
[a] Current model number (NIPG1500). Previous model number (NIPG1000). There is no difference in the delivery mechanism between these two models.

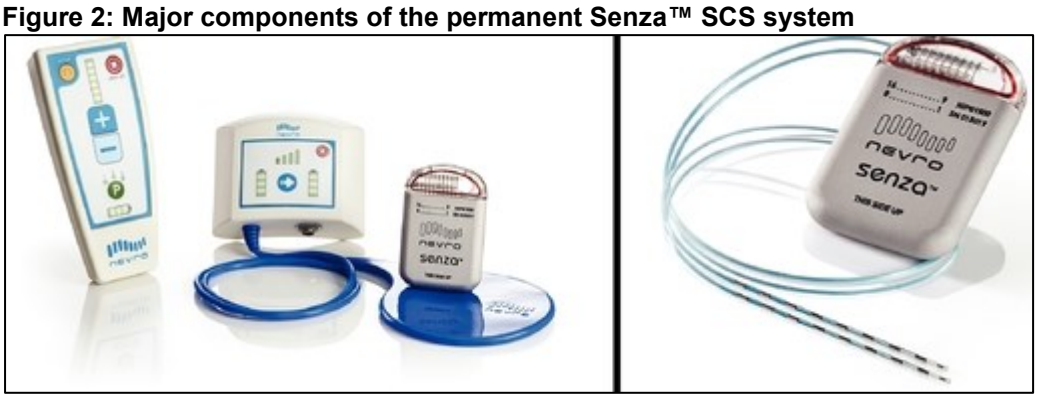
Figure 1: Lead placement for HF10™ therapy



Prior to permanent implantation of the Senza™ SCS system, a trial phase is performed. In this phase, the patient wears an external trial neurostimulator to determine whether the therapy provides a substantial reduction in pain, (a trial phase is also performed before permanent implantation of a traditional low-frequency SCS system).

The permanent Senza™ SCS system (referred to in this submission as HF10™ therapy from this point onwards) includes leads, a neurostimulator (with a rechargeable internal battery), a patient remote control and a battery recharger (Figure 2).

Figure 2: Major components of the permanent Senza™ SCS system



The neurostimulator and leads are inserted through a small incision in the patient's back under local or general anaesthesia. Post-implantation, the neurostimulator is controlled by the patient using the remote control to adjust the level of stimulation. The neurostimulator battery is rechargeable, with typical daily charging cycles of 30-40 minutes. Patients recharge the battery by placing the charging coil over the site of the implanted neurostimulator[b].

Regulatory approval for the Senza™ SCS system has been granted for a battery life of at least 10 years of continuous use (i.e. it is expected that the patient will not have to receive a new neurostimulator for at least 10 years).

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Chronic neuropathic pain

SCS is recommended by NICE Technology Appraisal Guidance (TAG)159 as a treatment option for patients with chronic pain of neuropathic origin, who continue to experience pain for at least 6 months despite conventional medical management (CMM) (2).

Due to the complex nature of chronic neuropathic pain, a multidisciplinary, integrated approach to management is undertaken (referred to as conventional medical management

[b] Traditional low-frequency SCS neurostimulators may be either implantable pulse generators (IPGs), which use a non-rechargeable or a rechargeable internal battery, or radio frequency devices, which receive energy in the form of radio frequency pulses from an external device powered by a rechargeable battery.

[CMM] throughout this submission). CMM typically includes pharmacological treatments, non-pharmacological interventions (e.g. physiotherapy, acupuncture, nerve blocks with injected local anaesthetics, transcutaneous electrical nerve stimulation) and psychological therapies (e.g. cognitive behavioural therapy, stress management, counselling).

Chronic pain is usually defined as any pain that persists beyond the normal time of healing (more than 3-6 months) (3). The pain can become progressively worse and recur intermittently. Very often chronic pain is considered to be neuropathic in origin (i.e. initiated or caused by, a primary lesion or dysfunction in the peripheral or central nervous system) either entirely or in part (mixed) (4).

Conditions that are most often considered to be of neuropathic or mixed neuropathic origin include, but are not limited to, failed back surgery syndrome (FBSS, persistent or recurring pain in the legs and/or back after lumbar surgery), radiculopathy (predominant leg or arm pain in the distribution of a nerve root and can also be a form of FBSS), or leg and/or back pain of non-mechanical nature with or without previous surgery.

Two randomised controlled trials (RCTs), the Kumar et al. (2007) trial, also known as the PROCESS study and the North et al. (2005) trial, were the primary sources of evidence for NICE TAG159 which recommends the use of SCS (5, 6) (see section 3.2 for detail). In these RCTs the study population consisted of patients with FBSS presenting with chronic pain (predominantly in the leg). The SENZA-RCT (HF10™ therapy) study population reflects the same patient population (i.e. patients with FBSS presenting with chronic pain); in the SENZA-RCT both leg and back pain were evaluated as separate regions of pain. The findings of the SENZA-RCT for the control arm (traditional low-frequency SCS) are consistent with previous prospective studies; however, there was a markedly superior clinical benefit with nearly twice the response rate for both leg and back pain with HF10™ therapy compared to traditional low-frequency SCS.

Other chronic neuropathic pain conditions include complex regional pain syndrome (CRPS)[c], phantom limb pain, central pain (e.g. post-stroke pain), diabetic neuropathy, and post-herpetic neuralgia (7). The UK prevalence of chronic neuropathic pain has been reported as 8.2% and 8.9% in two retrospective studies (8). However, not all patients with chronic neuropathic pain would warrant SCS treatment. According to Hospital Episode Statistics (HES), an estimated 1,137 SCS implantations took place in England in 2015[d] (9). It should be noted that this estimate includes all indications for SCS (i.e. leg, back, bowel and bladder pain). therefore SCS implantation for leg/back pain are lower than the estimated figure, however the exact figure is not publicly available.

Chronic neuropathic pain has a negative impact on health-related quality of life (HRQoL). Pain with neuropathic characteristics is generally more severe, and is associated with worse health in every measured dimension, compared to non-neuropathic pain. In a UK study among those with chronic neuropathic pain, 17% had HRQoL scores equivalent to 'worse than death' on the EQ-5D (10, 11). Aside from the physical consequences, neuropathic pain is often accompanied with psychological problems, including depression and anxiety (12). The aim of treatment for chronic neuropathic pain is to improve HRQoL by reducing pain and increasing the ability to function.

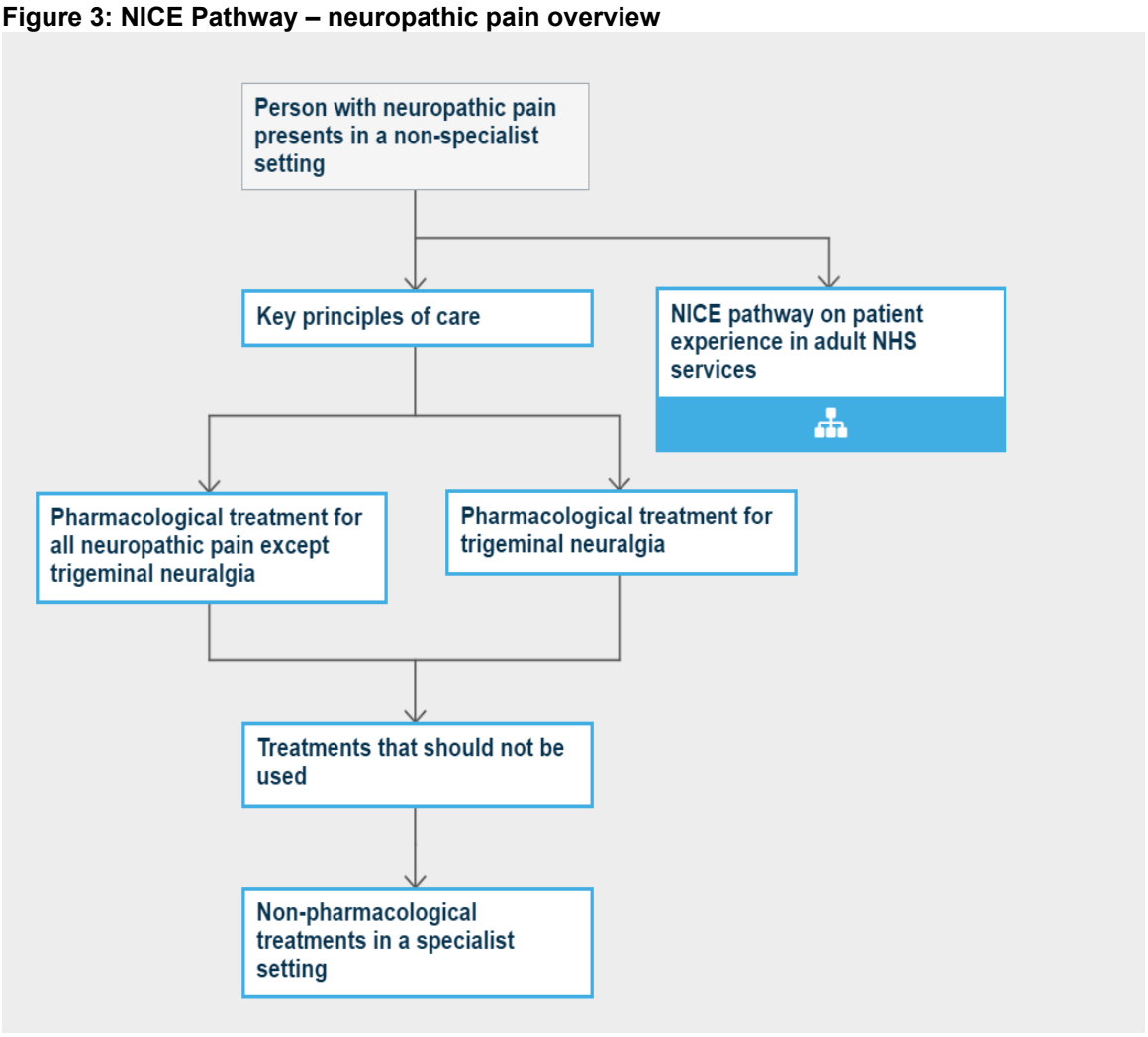
3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

The NICE Pathway for neuropathic pain Figure 3, provides an integrated view of everything NICE has published about this condition (13).

[c] Debilitating, painful condition in a limb (arms, legs, hands, or feet), usually after an injury or trauma to that limb.

[d] Admitted patient care procedures and interventions 2014/15. A48.3 insertion of neurostimulator adjacent to spinal cord (all procedures)

Figure 3: NICE Pathway – neuropathic pain overview



Source: NICE (13).

Sources informing the 'non-pharmacological treatments in a specialist setting' (latter part of the NICE Pathway) are:

- **NICE Technology Appraisal Guidance (TAG159). Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (2008)** (2)

This guidance recommends the use of SCS systems as follows:

1.1 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 CMM, and
- Who have had a successful trial of stimulation as part of the assessment specified in recommendation 1.3.

1.2 SCS is not recommended as a treatment option for adults with chronic pain of ischaemic origin except in the context of research as part of a clinical trial. Such research should be designed to generate robust evidence about the benefits of spinal cord stimulation (including pain relief, functional outcomes and quality of life) compared with standard care.

1.3 SCS should be provided only after an assessment by a multidisciplinary team experienced in chronic pain assessment and management of people with spinal cord stimulation devices, including experience in the provision of ongoing monitoring and support of the person assessed.

1.4 When assessing the severity of pain and the trial of stimulation, the multidisciplinary team should be aware of the need to ensure equality of access to treatment with spinal cord stimulation. Tests to assess pain and response to spinal cord stimulation should take into account a person's disabilities (such as physical or sensory disabilities), or linguistic or other communication difficulties, and may need to be adapted.

1.5 If different SCS systems are considered to be equally suitable for a person, the least costly should be used. Assessment of cost should take into account acquisition costs, the anticipated longevity of the system, the stimulation requirements of the person with chronic pain and the support package offered.

1.6 People who are currently using SCS for the treatment of chronic pain of ischaemic origin should have the option to continue treatment until they and their clinicians consider it appropriate to stop

- **NICE Clinical Guideline (CG173). Neuropathic pain in adults: pharmacological management in non-specialist settings (2013)** (14)

This guideline covers managing neuropathic pain with pharmacological treatments in adults in non-specialist settings (i.e. outside specialist pain management services). The guideline sets out how drug treatments for neuropathic pain differ from traditional pain management. The Guideline Development Group acknowledged that there are other pharmacological and non-pharmacological treatments that will be of benefit to people with neuropathic pain, within different care pathways in different settings.

- **Interventional Procedure Guidance (IPG450). Percutaneous electrical nerve stimulation for refractory neuropathic pain (2013)** (15)
- **Interventional Procedure Guidance (IPG382). Deep brain stimulation for refractory chronic pain syndromes (excluding headache) (2011)** (16)
- **Interventional Procedure Guidance (IPG85). Stereotactic radiosurgery for trigeminal neuralgia using the gamma knife (2004)** (17)

These IPGs recommend the use of the above procedures with normal arrangements for consent, audit and clinical governance.

The British Pain Society has also produced the following consensus document for the use of SCS:

- **British Pain Society. Spinal cord stimulation for the management of pain: recommendations for best clinical practice (2009)** (18)

This consensus document, produced in conjunction with the Society of British Neurological Surgeons, clarifies the rationale for the use of SCS for pain, gives guidance regarding patient selection, and makes recommendations regarding the context in which therapy should be delivered.

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

As oulined in section 3.1, due to the complex nature of chronic neuropathic pain, a multidisciplinary, integrated approach to management is undertaken (referred to as CMM throughout this submission).

Pharmacological treatments are part of CMM and include antidepressants, opioid analgesics and calcium channel alpha-2 delta ligands. CMM also includes non-pharmacological interventions (e.g. physiotherapy, acupuncture, nerve blocks with injected local anaesthetics, transcutaneous electrical nerve stimulation) and psychological therapies (e.g. cognitive behavioural therapy, stress management, counselling). The order in which therapies are selected varies across the UK, and different approaches may be delivered in parallel (7).

Treatment takes place in specialist and/or non-specialist settings that provide comprehensive assessment and multi-modal management of chronic neuropathic pain.

Some patients continue to experience chronic neuropathic pain despite appropriate CMM. For these patients SCS is a treatment option. NICE TAG159 (2) recommends SCS systems 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 CMM, and
- Who have had a successful trial of stimulation

As outlined in section B, HF10™ therapy is a superior alternative to traditional low-frequency SCS systems: it provides better outcomes for patients (19, 20). The patient population eligible for treatment with HF10™ therapy is the same population as that recommended by NICE TAG159 (outlined above). Therefore, HF10™ therapy would be included in the same position in the clinical pathway of care as traditional low-frequency SCS systems (2).

3.4 Please describe any issues relating to current clinical practice, including any uncertainty about best practice.

Despite the positive recommendation for the routine use of SCS systems from NICE TAG159 (2), England has the lowest yearly SCS implantation rates compared to other European countries (Table 2).

Table 2: Number of implantations in England versus other European countries/year

Country	SCS/million			
	2008	**2009**	**2010**	**2011**
Belgium	-	84.6	-	-
France	9.19	8.17	11.35	-
The Netherlands	-	-	-	54.3
Germany	-	-	11.7	-
England	-	-	11.0	10.7

Abbreviations: SCS, spinal cord stimulation.
Source: Vyawahare et al. (2014) (21).

3.5 Describe the new pathway of care incorporating the new, technology that would exist if the technology was adopted by the NHS in England.

If adopted by the NHS in England, HF10™ therapy would be used as an alternative to traditional low-frequency SCS systems, because it provides better outcomes for patients (19, 20). HF10™ therapy would be included in the same position in the pathway of care as traditional low-frequency SCS systems (see section 3.3 and NICE TAG159) (2).

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

There are no anticipated changes to the way services would be organised or delivered, as a result of introducing HF10™ therapy. HF10™ therapy would simply replace traditional low-frequency SCS systems, to provide better outcomes for patients.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

There are no additional tests, monitoring or administration requirements over and above usual clinical practice (i.e. practice using traditional low-frequency SCS systems).

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities or infrastructure are required for the claimed benefits to be realised.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

HF10™ therapy removes a potentially time consuming step in the operating theatre

Traditional low-frequency SCS systems require ‘paraesthesia mapping’ as part of the operation, both for the trial and during permanent implantation (section 2.2). This step is not required for HF10™ therapy because its mode of action is paraesthesia-free. Therefore, surgical procedure time is more predictable than traditional low-frequency SCS. In addition, since patients do not have to be woken up during the HF10™ therapy procedure for paresthesia mapping, the patient experience is less onerous.

HF10™ therapy reduces radiation exposure time and dosage

When implanting traditional low-frequency SCS systems, continuous fluoroscopy (real-time imaging using radiation) is needed due to the amount of lead manipulation required during paraesthesia mapping (22). This exposes patients, physicians, and procedural staff to radiation during the procedure. With HF10™ therapy, the leads are placed in a consistent fashion in the vertebra. This enables the use of pulsed fluoroscopy (delivering bursts of radiation at set intervals), instead of continuous fluoroscopy, reducing radiation exposure. In a recent study, the use of pulsed fluoroscopy with HF10™ therapy decreased exposure time and radiation dosage by more than 2-fold compared with continuous fluoroscopy (22). To put this into context, a typical chest X-ray involves a radiation exposure of 0.1 millisievert[e]. Thus, converting to pulsed fluoroscopy for a single HF10™ therapy procedure is equivalent to a reduced exposure of approximately 17 chest X-rays (22).

HF10™ therapy reduces opioid use and dosage

As outlined in section B:

- There was a significant reduction in opioid use in the SENZA-EU study: 86% of patients were taking some form of opioid at baseline, and this reduced to 57% at 24 months ($p<0.001$) with HF10™ therapy. The mean dose of oral morphine decreased from 84 mg/day at baseline to 27 mg/day at 24 months ($p<0.001$) (23)
- In the study by Rapcan et al. (2015), at 12 months 65% of patients had reduced their opioid use by half with HF10™ therapy (24)
- At 12 months, there was a 64% (72 mg/day) reduction in opioid use with HF10™ therapy compared with baseline, and three patients completely ceased their use of opioids ($p=0.0833$) in the study by Al-Kaisy et al. (2016) (25)

Previous large traditional low-frequency SCS system studies, such as the PROCESS study and North et al. study did not demonstrate a statistically significant reduction in opioid use (5, 6).

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

As outlined in section 3.9, the superior long-term outcomes of HF10™ therapy versus traditional low-frequency SCS (see section B), could potentially reduce follow-up attendances at pain clinics allowing for more efficient service configuration.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- **instructions for use**
- **CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity**
- **quality systems (ISO 13485) certificate (if required).**

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

HF10™ therapy was CE marked on 4th May 2010 (certificate CE 0086) to aid in the management of chronic, intractable pain of the truck and/or limbs, including unilateral or bilateral pain associated with the following:

- FBSS
- Intractable low back pain

[e] The scientific unit of measurement for radiation dose.

- Leg pain

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Details of regulatory approval for HF10™ therapy are provided in Table 3.

Table 3: Regulatory approval for HF10™ therapy

Area/country	Regulatory body	Date of regulatory approval
Europe	CE Marking	4th May 2010
Australia	Therapeutic Goods Administration	29th June 2011
USA	Food and Drug Administration	8th May 2015

Abbreviations: CE, Conformité Européenne; USA, United States of America.

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

HF10™ therapy has been launched in the UK.

4.5 If the technology has been launched in the UK provide information on the use in England.

Several major NHS pain centres in England have experience of using HF10™ therapy including:

- Southampton University NHS Foundation Trust
- Leeds Teaching Hospital NHS Foundation Trust
- North Bristol NHS Trust
- The Walton Centre NHS Foundation Trust, Liverpool
- Guy's and St Thomas' NHS Foundation Trust

However, HF10™ therapy remains under adopted despite the superior clinical outcomes achieved versus traditional low-frequency SCS systems.

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

A summary of ongoing HF10™ therapy studies is provided in Table 4.

Table 4: **Summary of HF10™ therapy ongoing studies**

Location/study name	Study design	Comparators	Patient population	Study aim	No. of patients	Duration	Expected completion
Belgium/Senza™ Registry	Registry	None	Leg and back pain	Confirm results in Belgium	120	12 months	Quarter 1/2018
Netherlands/FBSS	Prospective cohort	None	Leg and back pain	Confirm results in the Netherlands	55	12 months	Quarter 1/2018

Abbreviations: FBSS, failed back surgery syndrome.

A search of the websites www.isrctn.com and www.clinicaltrials.gov with the terms “Nevro,” “Senza,” and “high frequency” AND “spinal cord stimulation” was conducted to identify ongoing studies. Only one study in the population of interest to this submission was identified (see below), as this study is currently recruiting it is unlikely that results will be available in the next 12 months:

- **A prospective, open label, pilot study of patient outcomes following successful trial of high frequency spinal cord stimulation at 10,000 Hz (HF10™ therapy) leading to permanent implant compared to trial failure and standard care for the treatment of persistent low back pain of neuropathic origin (Maiden Back)** NCT02689375: prospective observational study comparing outcomes of patients with successful HF10 trials who go on to permanent implant of the Senza™ device with patients who have unsuccessful HF10 trials. Enrolled patients will have chronic low back pain of neuropathic origin with no history of spinal surgery; commenced February 2015, currently recruiting.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

No other form of assessment in the UK is currently underway or planned.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

There are no equality issues that Nevro Corporation are aware of relating to the patient population and the condition for which the technology is being used.

6.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

There are no equality issues that Nevro Corporation are aware of relating to the assessment of HF10™ therapy that requires special attention.

6.3 How will the submission address these issues and any equality issues raised in the scope?

N/A.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in Table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

A systematic literature review was conducted to identify relevant randomised controlled trials (RCTs) and non-RCTs on the use of HF10™ therapy to treat chronic pain of the legs and/or back. Additional hand-searching of the manufacturer's internal documentation was conducted to identify any unpublished studies. The hand-searching identified 46 published conference abstracts. Some of these abstracts were related to the studies presented in section B. These abstracts have not been reported in this submission as they were deemed to not add any additional evidence to that presented herein. Nevro Corporation can supply the abstracts to NICE for review if required.

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

Searches were conducted using the following databases: Medline (PubMed), the Cochrane Library (Wiley Online Library), Medline In-Process (Ovid), Scopus (Elsevier), and Embase (Elsevier). The searches were limited to publications from 2006 to present, reflecting the timeframe of the existence of the sponsor as a company (Nevro Corporation, Redwood City, CA, USA). Search terms combined "spinal cord stimulation" with descriptors specific to HF10™ therapy. The full search strategy is outlined in section 10.1.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Hand-searching of manufacturer's internal documentation was also undertaken to identify any relevant unpublished clinical data.

7.2 Study selection

Published studies

7.2.1 Complete Table 5 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Inclusion and exclusion selection criteria for published and unpublished studies are shown in Table 5.

Table 5: Selection criteria used for published and unpublished studies

Inclusion criteria	
Population	Patients with chronic neuropathic pain in the legs and/or back
Interventions	HF10™ therapy
Outcomes	• Trial stimulation success rate • Responder rates (proportion with ≥50% pain relief) • Pain scores (VAS, NRS) • HRQoL • Disability • Functioning • Patient satisfaction • Opioid usage • AE data
Study design	RCTs, non-RCTs, N ≥15 patients
Language restrictions	English language only
Search dates	2006-present
Exclusion criteria	
Interventions	Traditional low-frequency SCS
Outcomes	Costs and cost-effectiveness analysis
Study design	Case studies, editorials, reviews, letters, book chapters, conference abstracts

Abbreviations: AE, adverse event; HRQoL, health-related quality of life; NRS, numerical rating scale;, RCT, randomised controlled trial; SCS, spinal cord stimulation; VAS, visual analogue scale.

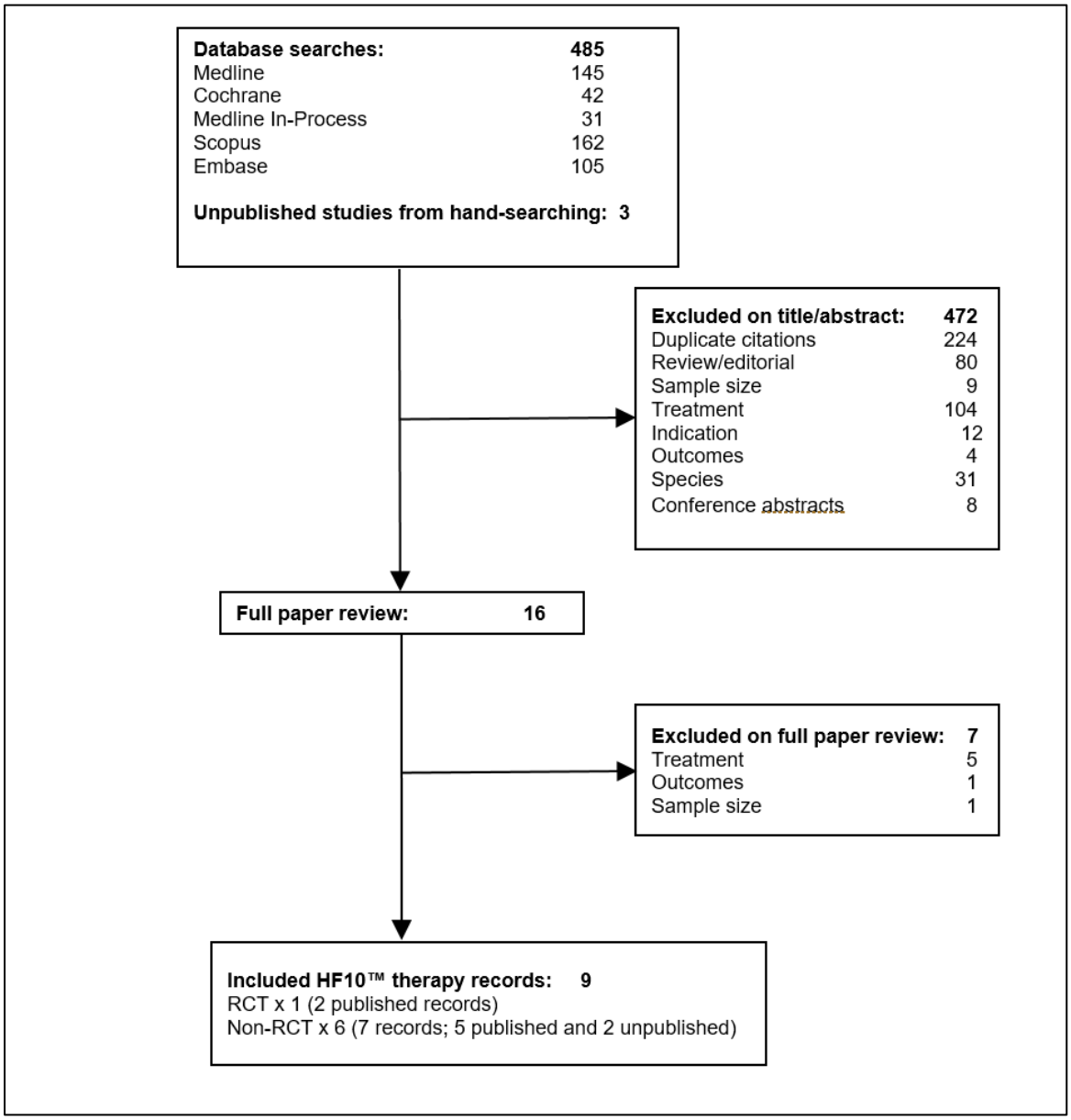
7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The database searches identified 485 published records and hand-searching of the manufacturer's database identified an additional three unpublished records (total 488 records). Following assessment of title and abstract 472 of the 488 records were excluded. Following assessment of 16 full-text records, seven records were excluded. A total of nine records covering seven studies (one RCT and six non-RCTs) were included in the final dataset (Figure 4). When the systematic literature review was conducted, two of the nine records included in the final dataset were unpublished (Al-Kaisy et al. (26)). These studies have since been published (25, 26). Two of the included nine records report results from one RCT

(Kapural et al. 2015 and Kapural et al. 2016) (19, 20) and seven records report results from six non-RCTs (23-29).

The schematic for the systematic literature review and hand-searching of the manufacturer's internal documentation is shown in Figure 4.

Figure 4: Schematic for the systematic review of published and unpublished studies



7.2.3 Complete Table 5 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Inclusion and exclusion selection criteria for unpublished studies are shown in Table 5.

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

See section 7.2.2 and Figure 4.

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in Table 5.

The systematic literature review of clinical evidence and hand-searching of the manufacturer's internal documentation identified 7 studies (9 records: 7 published and 2 unpublished) of relevance to this submission (Table 6). The 2 unpublished studies (Al-Kaisy et al. 2016 and De Carolis et al. 2017) have since been published and are therefore included in the table of published studies (Table 6).

Table 6: List of relevant published studies

Primary study reference	Study name (RCT/non-RCT)	Population	Intervention	Comparator
Kapural et al. (2015) (19) and Kapural et al. (2016) (20)	SENZA-RCT (RCT)	Chronic leg and back pain	HF10™ therapy	Traditional low-frequency SCS
Van Buyten et al. (2013) (27) and Al-Kaisy et al. (2014) (23)	SENZA-EU (non-RCT)	Chronic back pain with or without leg pain	HF10™ therapy	None
Russo et al. (2016) (28)	- (non-RCT)	Chronic pain back + leg, back only, head ± neck, neck ± arm/shoulder and leg only	HF10™ therapy	None
Tiede et al. (2013) (29)	- (non-RCT)	Chronic back pain with or without leg pain	HF10™ therapy	Traditional low-frequency SCS
Rapcan et al. (2015) (24)	- (non-RCT)	Chronic back pain with or without leg pain	HF10™ therapy	None
Al-Kaisy et al. (2016) (25)	- (non-RCT)	Chronic back pain with or without leg pain with no history of spinal surgery	HF10™ therapy	None
De Carolis et al. (2017) (26)	- (non-RCT)	Chronic back pain with or without leg pain	HF10™ therapy	None

Abbreviations: RCT, randomised controlled trial; spinal cord stimulation.

7.3.2 State the rationale behind excluding any of the published studies listed in Table 6.

None of the studies outlined in Table 6 have been excluded.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using Table 7 and Table 8 as appropriate. A separate table should be completed for each study.

The methodology for the relevant RCT (SENZA-RCT) is summarised in Table 7.

Table 7: Summary of methodology for the SENZA-RCT: Kapural et al. (2015) and Kapural et al. (2016)

Study name, author(s)	SENZA-RCT, Kapural et al. (2015) and Kapural et al. (2016) (19, 20)
Objective	To assess primarily non-inferiority and secondly superiority of HF10™ therapy compared with traditional low-frequency SCS†, in patients with chronic intractable leg and back pain
Location	USA (11 centres)
Design	Prospective, randomised
Duration of study	24 months
Sample size	Implanted N=171
Inclusion criteria	• Chronic intractable pain of the back and/or legs, refractory to CMM for a minimum of 3 months (previous treatments included pain medications, physical therapy, spinal injections, pharmacological, and behavioural treatment) • Average back pain intensity ≥5 cm out of 10 cm on the VAS‡ • Average leg pain intensity ≥5 cm out of 10 cm on the VAS • ODI version 2.1a score of 41-80 out of 100†† • Appropriate candidate for the surgical procedures required in the study
Exclusion criteria	• Active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain • Inability to comply with the intervention or evaluate treatment outcomes • Mechanical spine instability based on flexion/extension films of lumbar spine • Prior experience with SCS
Method of randomisation	Randomised in a 1:1 ratio to receive HF10™ therapy or traditional low-frequency SCS. Randomisation was stratified by gender and primary area of pain (either leg or back).
Method of blinding	Due to practical considerations, patients and investigators were not masked to the assigned treatment group
Intervention(s) (n =) and comparator(s) (n =)	Implanted N=171 (HF10™ therapy n=90, traditional low-frequency SCS n=81)

Baseline differences	Baseline pain scores were higher by a small amount for patients randomised to traditional low-frequency SCS. However, statistical analysis of the impact of baseline back and pain scores on treatment outcome demonstrates that these differences do not impact the conclusions drawn from the study.
Duration of follow-up, lost to follow-up information	Follow-up continued through 24 months. Included through 24 months: HF10™ therapy n=85, traditional low-frequency SCS n=71. Four patients (1 withdrew consent, 1 required an MRI, 1 death, 1 lost to follow-up) in the HF10™ therapy group and 9 patients (4 lost to follow-up, 2 deaths, 2 withdrew consent, 1 required an MRI) in the traditional low-frequency SCS group were not included beyond the 12-month analysis.
Statistical tests	Sample size for efficacy was based on a non-inferiority comparison of the primary endpoint between treatment groups. Using an exact binominal test for non-inferiority with a 10% non-inferiority margin, 80% statistical power, and a 0.05 one-sided significant level, a minimum of 77 patients per treatment group were required. In addition to classifying patients as responders or non-responders‡‡, patients were post-hoc classified as remitters or non-remitters. A pain remitter was defined as having a VAS pain score of ≤2.5 cm. Primary endpoint analyses were performed on ITT, per protocol and permanent implant populations. Secondary outcomes were successfully evaluated for tests of non-inferiority (hierarchical closed-test approach) with one-sided 0.05 significance levels until statistical significance level was not reached. For each outcome tested, if non-inferiority was demonstrated, then superiority was subsequently assessed post hoc with a two-sided 0.05 significance level and Bonferroni correction for multiple comparisons within each family of outcomes at each time point. A conservative two-sided *P* value of 0.002 or less (0.05/24) was required for individual post hoc tests of superiority for primary and secondary outcomes. For AEs proportions were compared between treatment groups using Fisher exact tests with a two-sided significance level of 5%. Longitudinal results were assessed using repeated-measures ANOVA.
Primary outcomes (including scoring methods and timings of assessments)	Composite of safety and efficacy; percentage of patients who respond to SCS therapy for back pain (≥50% reduction in VAS score), without a stimulation-related neurological deficit at 3 months post-device activation
Secondary outcomes (including scoring	• Percentage of patients responding to back pain (6, 9, 12, 18, 24 months) • Percentage of patients responding to leg pain (3, 6, 9, 12, 18, 24 months)

methods and timings of assessments)	• ODI categorisation (%), (3, 6, 12, 18, 24 months) • Opioid analgesic usage (3, 6, 9, 12 months) • GAF (3, 6, 12 months) • PGIC (3, 12, 18, 24 months) • CGIC (3, 12, 18, 24 months) • Patient satisfaction scores (3, 12, 18, 24 months) • AEs (3, 6, 9, 12, 18, 24 months)

Abbreviations: AEs, adverse events; CGIC, clinician global impression of change; CMM, conventional medical management; GAF, global assessment of functioning; ITT, intention-to-treat; ODI, Oswestry disability index; MRI, magnetic resonance imaging; PGIC, patient global impression of change; SCS, spinal cord stimulation; USA, United States of America; VAS, visual analogue scale.

† Precision Plus System; Boston Scientific, USA.

‡ On the VAS, a score of 0 = no pain and 10 = very severe pain.

†† A score of 40 to 60=severe disability and 60-80 = crippled.

‡‡ Patients that did not have a successful trial phase were considered non-responders for the ITT and per protocol analyses.

The methodology for relevant observational studies is summarised in Table 8 to Table 13.

Table 8: Summary of methodology for the observational study, SENZA-EU: Van Buyten et al. (2013) and Al-Kaisy et al. (2014)

Study name, author(s)	**SENZA-EU, Van Buyten et al. (2013) and Al-Kaisy et al. (2014) (27) (23)**
Objective	Quantify the efficacy and safety of HF10™ therapy for the treatment of patients with a primary diagnosis of chronic intractable back pain with or without leg pain
Location	Belgium (1 centre) and the UK (1 centre)
Design	Prospective, single-arm, multicentre, open-label
Duration of study	24 months
Patient population	Patients with predominant chronic intractable pain of the low back with or without leg pain
Sample size	Implanted N=72
Inclusion criteria	• Failed to respond to at least 6 months of CMM including pharmacological treatment, physical therapy, epidural injections and/or radiofrequency therapy • Have a primary diagnosis of chronic back pain (defined as lumbo-sacral pain) with or without leg pain with ≥5 out of 10 cm on the VAS (average score over the last 30 days) • Able to provide consent • ≥18 years • Able to comply with study procedures, visits, and assessments

Study name, author(s)	SENZA-EU, Van Buyten et al. (2013) and Al-Kaisy et al. (2014) (27) (23)
Exclusion criteria	• Obvious mechanical instability related to pain (diagnosed by imaging taken within the past 12 months) • Malignancies • Life expectancy of <1 year • Systematic infection • Have any active implanted device whether turned off or on • Already participating in another clinical study • Pregnant/lactating or not using adequate birth control • Untreated major psychiatric comorbidity, serious drug related behaviour issues • Bleeding complications or coagulopathy issues • Immunocompromised patients at risk for infection or other issues • Insulin-dependent diabetic who is not controlled through diet and/or medication
Intervention(s) (n =) and comparator(s) (n =)	Implanted N=72 (HF10™ therapy n=72, comparator N/A)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were pro-actively assessed following permanent implant. Sixty-five of the 72 implanted patients were available for data collection at 24 months. Four patients did not consent to continued data collection beyond 6-months, two were explanted due to sub-optimal pain relief, and one patient was withdrawn from the study due to painful pelvic pathology which interfered with the study.
Statistical tests	Two-tailed paired *t*-test was used to analyse continuous variables, such as VAS. A *P* value of ≤5% ($p<0.05$) was considered to be statistically significant.
Outcomes (including scoring methods and timings of assessments)	• Back pain VAS score (3, 6, 12, 24 months) • Leg pain VAS score (3, 6, 12, 24 months) • Sleep disturbance as assessed by the subjective number of awakenings per night (3, 6, 12, 24 months) • ODI categorisation (%), (3, 6, 12, 24 months) • Opioid analgesic usage (3, 6, 12, 24 months) • Patient satisfaction using a 5-point scale and whether they would recommend it to others (6, 12, 24 months)

Abbreviations: Abbreviations: CMM, conventional medical management; N/A, not applicable; ODI, Oswestry disability index; UK, United Kingdom; VAS, visual analogue scale.

Table 9: Summary of methodology for the observational study: Russo et al. (2016)

Author(s)	Russo et al. (2016) (28)
Objective	Report on the effectiveness of HF10™ therapy for a wide range of intractable pain conditions (including back only, leg only, back and leg, head ± neck pain, neck ± shoulder/arm pain, and other complex pain patterns)
Location	Australia (3 centres)

Author(s)	Russo et al. (2016) (28)
Design	Retrospective data collection, multicentre
Duration of study	6 months
Patient population	Patients with chronic intractable pain distributions, including back only, leg only, back and leg, head ± neck pain, neck ± shoulder/arm pain, and other complex pain patterns
Sample size	Implanted N=186
Inclusion criteria	N/A as retrospective data collection, no formal inclusion criteria
Exclusion criteria	N/A as retrospective data collection, no formal exclusion criteria
Intervention(s) (n =) and comparator(s) (n =)	Implanted (HF10™ therapy n=186, comparator N/A)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Retrospective data
Statistical tests	Statistical significance was determined by a paired samples *t*-test with a *P* value of <0.05 considered significant
Outcomes (including scoring methods and timings of assessments)	• Overall pain as assessed by the NPRS† for all patients, back and leg, back only, neck ± arm/shoulder, head ± neck and patients who had previously failed traditional stimulator treatment (initial, post-trial, 3 and 6 months' post-implant, as available in medical records) Additional functional outcome measures were collected at 2 of the 3 sites: • ODI categorisation (%), (initial, post-trial, 3 and 6 months' post-implant, as available in medical records) Activity tolerances (minutes), sitting, standing, and walking (initial, post-trial, 3 and 6 months' post-implant, as available in medical records)

Abbreviations: N/A, not applicable; NPRS, numerical pain rating scale; ODI, Oswestry disability index.
† NPRS 0-10, where 0 = no pain and 10 = worst imaginable pain.

Table 10: Summary of methodology for the observational study: Tiede et al. (2013)

Author(s)	Tiede et al. (2013) (29)
Objective	To examine the feasibility of HF10™ therapy in patients with chronic predominant back pain with or without leg pain
Location	USA (5 centres)
Design	Prospective, multicentre, open-label

Author(s)	Tiede et al. (2013) (29)
Duration of study	4 days with investigational stimulation (HF10™ therapy), connected to the previously implanted percutaneously placed commercially available trial leads (conventional stimulation)
Patient population	Chronic predominant back pain with or without leg pain
Sample size	Implanted N=24
Inclusion criteria	• ≥18 years • Chronic pain predominantly in the back with an intensity of ≥5 cm out of 10 cm on the VAS • Already confirmed as a candidate for conventional SCS therapy • Capable of giving informed consent • Able to comply with the requirements of the study visit, follow-up phone visits and self-assessment questionnaires
Exclusion criteria	• Complication(s) with temporary percutaneous lead placement from the prior conventional SCS "Trial Phase" • Systemic infection • Any other implanted device whether turned on or off • Participating in another study • Pregnant/lactating or not using adequate birth control • Untreated major psychiatric comorbidity • Serious drug-related behaviour issues • Bleeding complications or coagulopathy • Immunocompromised patients at risk for infection • Insulin-dependent diabetes not controlled through diet and/or medication
Intervention(s) (n =) and comparator(s) (n =)	HF10™ therapy, investigational stimulation (n=24), comparator, conventional stimulation (n=24).
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were pro-actively assessed at Day 4 with investigational stimulation (post-conventional stimulation) Of the 24 patients implanted (conventional stimulation) none were lost to follow-up (investigational stimulation)
Statistical tests	Analysis of VAS data was performed using two-tailed *t*-tests with significance levels indicated for each data set

Author(s)	Tiede et al. (2013) (29)
Outcomes (including scoring methods and timings of assessments)	• Overall pain VAS score with conventional stimulation and investigational stimulation (conclusion of investigational stimulation Day 4) • Back pain VAS score with conventional stimulation and investigational stimulation (conclusion of investigational stimulation Day 4) • Patient preference (conclusion of investigational stimulation Day 4) • AEs (conclusion of investigational stimulation Day 4)

Abbreviations: AEs, adverse events; N/A, not applicable; SCS, spinal cord stimulation; USA, United States of America; VAS, visual analogue scale.

Table 11: Summary of methodology for the observational study: Rapcan et al. (2015)

Author(s)	Rapcan et al. (2015) (24)
Objective	Report on clinical experience with HF10™ therapy for FBSS in patients with predominant low back pain with or without leg pain
Location	Slovakia (4 centres)
Design	Non-randomised, prospective, multicentre
Duration of study	12 months
Patient population	Chronic back pain with or without leg pain
Sample size	Implanted N=21
Inclusion criteria	• ≥18 years • Primary diagnosis of chronic back pain with or without leg pain, intensity of ≥6 cm out of 10 cm on the VAS • Failure of CMM including pharmacological treatment, physical therapy, epidural injections • Ability to provide consent and comply with study procedures, visits, and evaluations
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	Implanted N=21 (HF10™ therapy n=21, comparator N/A)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Pro-active follow-up immediately after implantation and at 3, 6, 9, and 12 months after implantation. Of the 21 patients implanted none were lost to follow-up.
Statistical tests	Differences in means were calculated using a two-sided *t*-test with a 95% confidence interval, the level of significance was 0.01.

Author(s)	Rapcan et al. (2015) (24)
Outcomes (including scoring methods and timings of assessments)	• Back pain VAS score (immediately after implantation and at 3, 6, 9, and 12 months after implantation) • Performance status (immediately after implantation and at 3, 6, 9, and 12 months after implantation) • Patient satisfaction scores (immediately after implantation and at 3, 6, 9, and 12 months after implantation) • Opioid analgesic usage (immediately after implantation and at 3, 6, 9, and 12 months after implantation)

Abbreviations: CMM, conventional medical management; FBSS, failed back surgery syndrome; N/A, not applicable; VAS, visual analogue scale.

Table 12: Summary of methodology for the observational study: Al-Kaisy et al. (2016)

Author(s)	Al-Kaisy et al. (2016) (25)
Objective	Explore the effectiveness of HF10™ therapy for the treatment of chronic axial low back pain in patients with or without leg pain who have not had spinal surgery
Location	UK (1 centre)
Design	Preliminary, single-centre, prospective, proof-of-concept
Duration of study	12 months
Patient population	Surgically naïve patients with chronic, medical refractory, predominantly axial, lower back pain with or without leg pain unsuitable for spinal surgery
Sample size	Implanted N=20
Inclusion criteria	• ≥18 and ≤65 years • Symptoms of axial low back pain for ≥6 months, with a intensity of ≥5 cm out of 10 cm on the VAS • Predominant back pain, with VAS back scores being >2 cm greater than leg pain if present • Failure to respond to CMM including where appropriate intensive physical rehabilitation programme and facet joints or medical branches local anaesthetic infiltrations • No history of previous spinal surgery • Clear of any spinal pathology that would lead to recommendation for any evidence-based surgical intervention • Degenerative disc disease confirmed by MRI and/or by discography • On stable dose (≥6 months) of analgesic medications, including opioids and anti-neuropathic drugs

Author(s)	Al-Kaisy et al. (2016) (25)
Exclusion criteria	• Not able to comply with study related requirements, procedures, and visits • Active alcohol, marijuana, recreational or prescription drug abuse or dependence or unwilling to stop/reduce excessive inappropriate medication • A medical pain or condition in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study outcomes • Mechanical spin instability • Current diagnosis of progressive neurologic disease • Immunocompromised and at increased risk for infection • Metastatic malignant disease or active local malignant disease • Pregnant or not using adequate birth control • An existing drug pump, an existing SCS system, and/or another active implantable device
Intervention(s) (n =) and comparator(s) (n =)	Implanted N=20 (HF10™ therapy n=20, comparator N/A)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Pro-active follow-up at 1, 3, 6, and 12 months after permanent implantation. Of the 20 patients implanted none were lost to follow-up.
Statistical tests	Statistical significance was accepted as a $p<0.05$ level. An analysis of variance including the period (follow-up visit) as repeated factor was applied to each of the analysed variables; pairwise comparisons of periods were also conducted. The probability value and 95% confidence limits for differences between arithmetic means were adjusted by the Dunnett method. If the analysed variable was not homogenous (Levene test) or variances relative to periods were not equal, the variable was $\log_e$-transformed.
Outcomes (including scoring methods and timings of assessments)	• Back pain VAS score (1, 3, 6, and 12 months) • Leg pain VAS score (1, 3, 6, and 12 months) • ODI categorisation (%), (1, 3, 6, and 12 months) • Patient satisfaction scores (1, 3, 6, and 12 months) • Sleep disturbance as assessed by average sleep hour's per night, average pain-induced sleep disturbances per night (1, 3, 6, and 12 months) • SF-36 and EQ-5D TTO (1, 3, 6, and 12 months) • Number of patients employed (1, 3, 6, and 12 months) • Opioid analgesic usage (1, 3, 6, and 12 months) • AEs

Abbreviations: AEs, adverse events; CMM, conventional medical management; EQ-5D, EuroQoL-5 dimension; MRI, magnetic resonance imaging; N/A, not applicable; ODI, Oswestry disability index; SCS, spinal cord stimulation; SF-36, short-form 36; TTO, time-trade-off; VAS, visual analogue scale.

Table 13: Summary of methodology for the observational study: De Carolis et al. (2017)

Author(s)	De Carolis et al. (2017) (26)
Objective	Given the absence of paraesthesia with HF10™ therapy it is not known if HF10™ therapy follows the same technical requirements as traditional low-frequency SCS. Paraesthesia responses were analysed to determine if 10 kHz paraesthesia-free SCS was dependent upon paraesthesia-pain overlap and position relative to physiologic midline
Location	USA (10 centres), Italy (1 centre)
Design	Multicentre (sub-study of the SENZA-RCT and a single centre using HF10™ therapy through commercial means)
Duration of study	24 months
Patient population	Patients successfully using HF10™ therapy with chronic intractable low back with or without leg pain
Sample size	Implanted N=61
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Intervention(s) (n =) and comparator(s) (n =)	Implanted N=61 (HF10™ therapy n=41 already participating in the SENZA-RCT and n=20 single centre in Italy, comparator N/A)
Baseline differences	N/A
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Most of the paraesthesia measurements were made at the 24-month follow-up appointment in the SENZA-RCT. In Italy follow-up visits ranged from 0.25-27 months' post implant. Of the 61 patients implanted none were lost to follow-up.
Statistical tests	To determine if there was a relationship between LF paraesthesia-pain overlap from HF10™ therapy sites and HF10™ efficacy, a linear regression analysis was performed using Real Statistics Resource Pack (release 4.3), Microsoft Excel. Summary statistics of pain relief were calculated for the medial and lateral groups and compared (Mann-Whitney U, 2-tailed).
Outcomes (including scoring methods and timings of assessments)	VAS pain score† (not stated)

Abbreviations: LF, low-frequency; N/A, not applicable; SCS, spinal cord stimulation; USA, United States of America.

† Non-technical outcome, other outcomes were technical related and not relevant to report in this submission.

The study by De Carolis et al. was primarily designed to assess the technical factors of HF10™ therapy. It has been included in this submission as pain relief was an outcome in the study (26).

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Data for the SENZA-RCT has been taken from Kapural et al. (2015) and Kapural et al. (2016) (19, 20). Kapural et al. (2015) reports results up to 12 months and Kapural et al. (2016) reports results through 24 months (19, 20).

Data from the SENZA-EU study have been taken from Van Buyten et al. (2013) and Al-Kaisy et al. (2014) (27) (23). Van Buyten et al. (2013) reports results up to 6 months and Al-Kaisy et al. (2014) reports through 24 months (27) (23).

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

A summary of the patient populations in the studies is provided in Table 14. There are no major differences between patient populations. The majority of patients across the studies had FBSS. Most studies were observational and aside from the SENZA-RCT (19, 20) and Tiede et al. (2013) (29), were single-arm.

Table 14: Summary of patient populations

Study name, author(s)	Study population
SENZA-RCT Kapural et al. (2015) and Kapural et al. (2016) (19, 20)	Adult patients with chronic leg pain and back pain • Average back pain intensity ≥5 cm out of 10 cm on the VAS • Average leg pain intensity ≥5 cm out of 10 cm on the VAS • CMM failure (3 months) • 77.1% of patients had FBSS
SENZA-EU Van Buyten et al. (2013) (27) and Al-Kaisy et al. (2014) (23)	Adult patients with chronic back pain with or without leg pain • Average back with or without leg pain intensity ≥5 cm out of 10 cm on the VAS • CMM failure (6 months) • 80.7% of patients had FBSS, including 14 patients who had previously failed traditional low-frequency SCS • 86.7% of patients had predominant back pain
Russo et al. (2016) (28)	Adult patients with chronic pain (back only, leg only, back and leg, head and/or neck pain, neck and/or shoulder/arm pain, and other complex patterns) • 46.5% (most common) had predominant back and leg pain

	• 18% had predominant back pain • 29.7% of patients had previously failed traditional low-frequency SCS or PNFS (although in 37.5% this was not recorded)
Tiede et al. (2013) (29)	Adult patients with chronic back pain with or without leg pain • Average back pain intensity ≥5 cm out of 10 cm on the VAS • Confirmed as a candidate for traditional low-frequency SCS • 87.5% of patients had FBSS • All patients had predominant back pain and 15 patients (62.5%) had additional leg pain
Rapcan et al. (2015) (24)	Adults patients with chronic back pain with or without leg pain • Average back with or without leg pain intensity ≥6 cm out of 10 cm on the VAS • CMM failure • All patients had FBSS
Al-Kaisy et al. (2016) (25)	Adult patients with chronic back pain with or without leg pain with no history of spinal surgery • Average back pain intensity of ≥6 cm out of 10 cm on the VAS • CMM failure
De Carolis et al. (2017) (26)	Adults with chronic back pain with or without leg pain (sub study of SENZA-RCT)

Abbreviations: CMM, conventional medical management; FBSS, failed back surgery syndrome; RCT, randomised controlled trial; SCS, spinal cord stimulation; VAS, visual analogue scale.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Subgroup analyses were undertaken in the studies as follows:

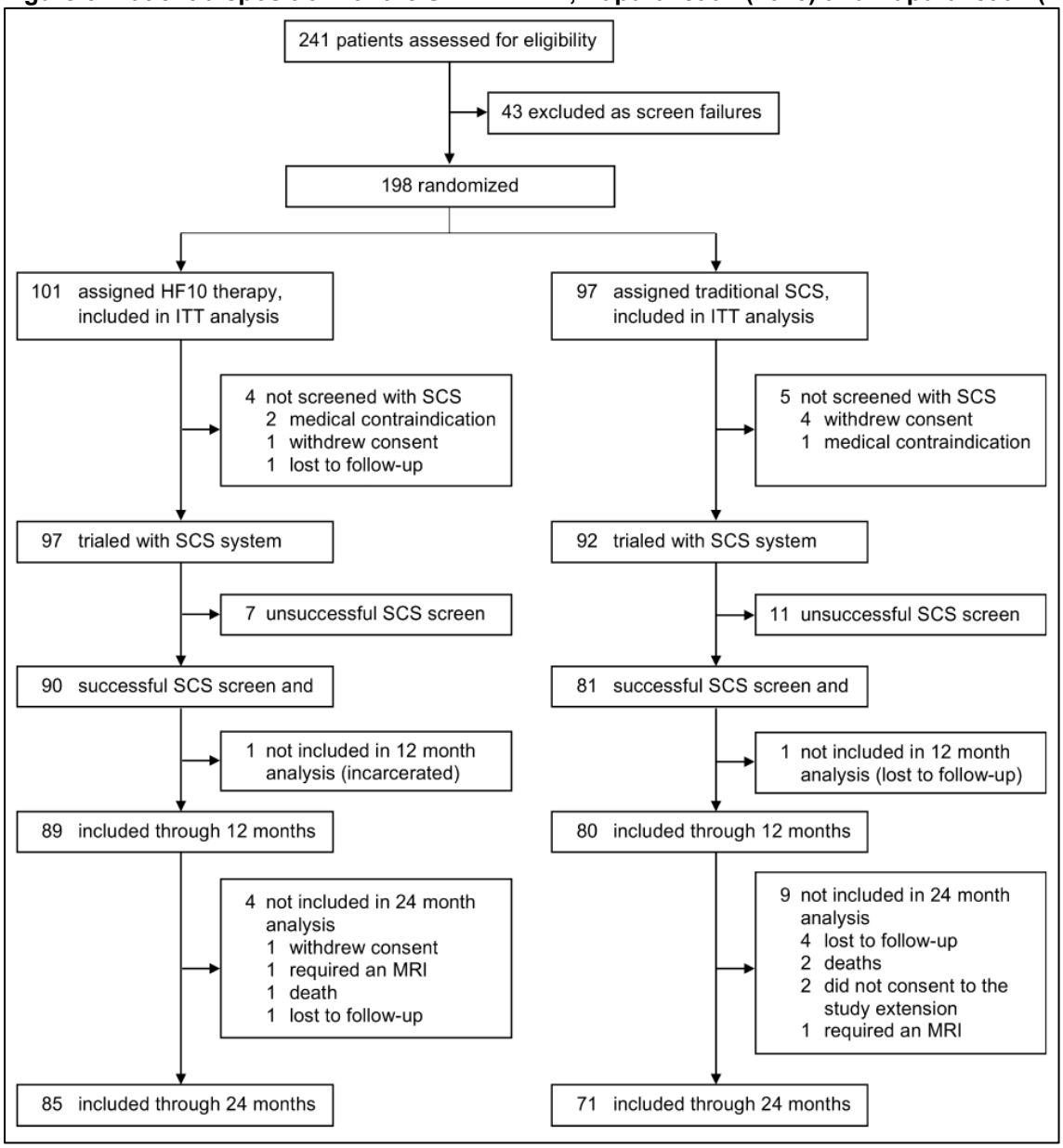
- SENZA-RCT study: patients were post-hoc classified as remitters or non-remitters. Results are presented in section 7.6.1, Table 22 (19, 20)
- SENZA-EU study: patients with FBSS, patients with past history of surgery, and patients who had previously failed traditional low-frequency SCS (23) (27)
- Russo et al. (2016): patients with leg and back pain, patients with back pain only, patients with neck and or arm/shoulder pain, patients with head and/or neck pain (28). Results are only presented in this submission that are relevant (leg and back pain and back only)
- Rapcan et al. (2015): describes a “special” subgroup. During the 12 months follow-up, an unexpected group of patients emerged who were unable to maintain satisfactory

pain relief with neither HF10™ therapy or traditional low-frequency SCS alone. These patients (n=4) had to switch between HF10™ therapy and traditional low-frequency SCS every 4-5 weeks (24)

Information was not provided in the publications regarding the rationale or if the subgroup analyses were pre-planned or post-hoc for any studies except the SENZA-RCT publication (19, 20). None of the other studies reported on subgroups.

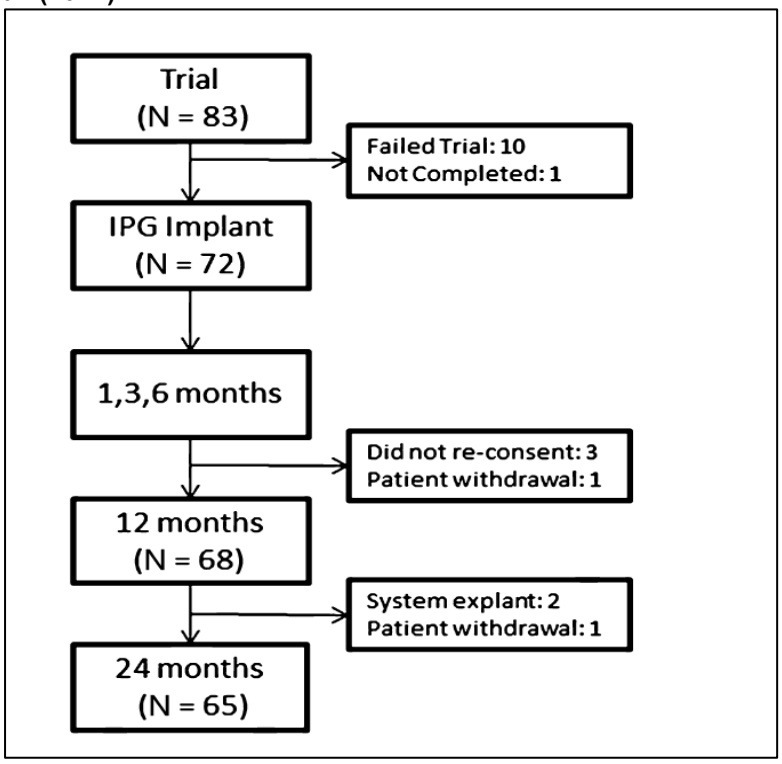
7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Figure 5: Patient disposition for the SENZA-RCT, Kapural et al. (2015) and Kapural et al. (2016)



Abbreviations: ITT, intention-to-treat; MRI, magnetic resonance imaging; SCS, spinal cord stimulation.
Source: Kapural et al. (2016) (20).

Figure 6: Patient disposition for the SENZA-EU study, Van Buyten et al. (2013) and Al-Kaisy et al. (2014)



Abbreviations: IPG, implantable pulse generator.
Source: Al-Kaisy et al. (2014) (23).

Table 15: Patient disposition for other non-RCTs

Study	Patient disposition
Russo et al. (2016) (28)	Of the 256 patients that trialled HF10™ therapy, 189 reported a positive trial and were implanted. As data was collected retrospectively, missing data points were unavoidable. The publication reports (n=) in the figures for the various outcomes.
Tiede et al. (2013) (29)	Enrolled: n=25 Completed study: n=24 One patient withdrew due to a non-study related flare up of pre-existing cervicalgia
Rapcan et al. (2015) (24)	Enrolled: n=21 Completed study: n=21
Al-Kaisy et al. (2016) (25)	Enrolled: n=21 Completed study: n=20 One patient did not successfully complete the HF10™ therapy trial
De Carolis et al. (2017) (26)	Enrolled: n=61 Completed study: n=61

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Details of and the rationale for, patients that were lost to follow-up or withdrew from the studies are provided in Figure 5, Figure 6 and Table 15.

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in Table 16 and Table 17.

Table 16: Quality assessment SENZA-RCT, Kapural et al. (2015) and Kapural et al. (2016)

Study name	**SENZA-RCT: Kapural et al. (2015) and Kapural et al. (2016) (19, 20)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomisation stratified by sex and primary pain area (back vs. leg), central administration by an independent statistician with each site randomly assigned alternating blocks of 2, 4, and 6 with frequencies 0.25, 0.50, and 0.25, respectively. Patients were randomised 1:1 to the treatment groups.
Was the concealment of treatment allocation adequate?	Yes	Due to paraesthesia induction by traditional, low frequency SCS and technical differences between the two devices, the patients and investigators could not be blinded to the assigned treatment group throughout the study; however, consecutive patients within each site-specific strata block were assigned to a treatment group sequentially to preserve blinding of study sites to the upcoming treatment group allocations. Sites were notified of the randomised treatment assignment after conducting the patient's baseline evaluations.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The treatment groups were similar for average age, gender, years since diagnosis, type of diagnosis, history of spinal surgery, opioid use, and proportion with predominant back pain. Baseline pain scores, both back and leg, were slightly higher for the traditional, low frequency SCS group; however, subsequent statistical analysis determined that the baseline differences did not impact the conclusions drawn from the study.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of	No	The initial treatment allocation was performed at a centralised location and concealed from providers, participants, and outcome assessors until after baseline assessments were collected, minimizing the potential for selection bias. Blinding was not possible for the duration of the study due to apparent differences between the two study devices, resulting in the potential for performance and/or detection biases. The authors state that the

bias (for each outcome)?		effect of lack of blinding on the outcomes is not known, but the protocol followed best practices for comparative efficacy trials. There is little reason to believe that site personnel or study participants would have a competing interest that would bias the study outcomes. The authors disclosed their potential conflicts of interest in the publications.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	The following data are reported as a percentage of total patients randomised to each treatment group: • Trial stimulation success: HF10™ therapy: 89%; Traditional low-frequency SCS: 84% • 3-month data collected: HF10™ therapy: 89%; Traditional low-frequency SCS: 84% • 12-month data collected: HF10™ therapy: 88%; Traditional low-frequency SCS: 82% • 24-month data collected: HF10™ therapy: 84%; Traditional low-frequency SCS: 73% All patients with a successful trial stimulation period were eligible to receive a permanent implant and were followed for 12 months. Each treatment group lost 1 subject between the 3 and 12 month visits. The study design originally included 12 months of follow-up, but patients were asked to re-consent to extend follow-up to 24 months. Retention rates remained high through 24 months of follow-up; however, there was a higher attrition rate for the traditional SCS group with 9 patients lost to follow-up, compared with 4 patients from the HF10™ therapy group. Reasons were provided in the Kapural 2016 publication for each subject lost to follow-up.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Data are reported for each outcome measure detailed in the methods sections.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT analysis was reported for the primary endpoint of responder rates at 3-month follow-up. Patients with unsuccessful trial stimulation were included in the ITT analysis as non-responders. Statistical tests of non-inferiority and superiority were based on the ITT population.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

Abbreviations: ITT, intention-to-treat; SCS, spinal cord stimulation.
Source: Kapural et al. (2015) and Kapural et al. (2016) (19, 20).

Table 17: Quality assessment SENZA-EU, Van Buyten et al. (2013) and Al-Kaisy et al. (2014)

Study name	**SENZA-EU: Van Buyten et al. (2013) and Al-Kaisy et al. (2014)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients with chronic, intractable back pain were recruited with ethics committee approval at 2 European centres. Patients with mechanical instability were excluded.
Was the exposure accurately measured to minimise bias?	Yes	Patients underwent a trial of HF10™ therapy for 14-30 days to assess efficacy, those with ≥50% reduction in pain from baseline proceeded to permanent implant.
Was the outcome accurately measured to minimise bias?	Yes	Outcome measures included the visual analogue scale (VAS), sleep disturbances, Oswestry Disability Index (ODI), and patient satisfaction.
Have the authors identified all important confounding factors?	N/A	Single-arm study with no control group.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	Comparison of outcomes in patients pre and post implantation of HF10.
Was the follow-up of patients complete?	Yes	Data were reported for all implanted patients at 6 months (N=72), 94% of implanted patients at 12 months (N=68), and 90% of implanted patients at 24 months (N=65).
How precise (for example, in terms of confidence interval and p values) are the results?		95% confidence intervals not reported. However, P-values (P<0.001 for back and leg pain) indicate statistically significant pre versus post HF10™ differences.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.		

Abbreviations: N/A, not applicable.
Source: Van Buyten et al. (2013) and Al-Kaisy et al. (2014) (23, 27).

Table 18: Quality assessment, Russo et al. (2014)

Study name	Russo et al. (2014) (28)	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Retrospective chart reviews of patients with a variety of chronic pain conditions treated with HF10™ therapy at 3 Australian medical centres over 2.5 years. Consent obtained from each subject prior to data extraction.
Was the exposure accurately measured to minimise bias?	No	Each subject underwent 7-14 day trial stimulation with HF10™ therapy to assess efficacy prior to permanent implant; however, there was no strict definition of trial success, which is typically defined as ≥50% pain relief. Patients went on to permanent implant if they reported significant improvement in function or were able to reduce medication intake, or reported "some other measure of success that was deemed clinically appropriate."
Was the outcome accurately measured to minimise bias?	Yes	Outcomes measured were numerical pain rating scale (NPRS), pain distribution, prior SCS history, Oswestry Disability Index (ODI), ability to sit, stand, and walk, and patient report of pain relief and pain medication reduction.
Have the authors identified all important confounding factors?	N/A	Single-arm study with no control group.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Pooled data from a large sample size (N=256) at 3 sites over 2.5 years, representative patient population in clinical experience, each patient acted as their own control, discussion of potential negative bias from lack of pain relief threshold for trial success.
Was the follow-up of patients complete?	No	As a retrospective chart review, data collection was not rigorous or uniform among the 3 sites, few patients had a full data set of pain, disability, and activity tolerance scores, large attrition rate over time (N=189 implanted, N=125 with data at 6 months).
How precise (for example, in terms of confidence interval and p values) are the results?		95% confidence intervals not reported. However, P-values (P<0.05 to P<0.001 for pain and functional outcomes) indicate statistically significant pre versus post HF10™ differences.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.		

Abbreviations: N/A, not applicable; SCS, spinal cord stimulation.
Source: Russo et al. (2014) (28).

Table 19: Quality assessment, Tiede et al. (2013)

Study name	**Tiede et al. (2013) (29)**	
Study question	**Response (yes/no/not clear/NA)**	**How is the question addressed in the study?**
Study question	Yes	Patients with predominant axial back pain were recruited at 5 USA sites.
Was the cohort recruited in an acceptable way?	Yes	Patients underwent a temporary trial stimulation with HF10™ therapy to assess efficacy.
Was the exposure accurately measured to minimise bias?	Yes	Outcome measures included visual analogue scale (VAS), subjective descriptions, and patient preference.
Was the outcome accurately measured to minimise bias?	Yes	Short duration, small sample size, non-randomised, increased attention to patients during HF10™ therapy trial, prior traditional SCS trial, lack of paraesthesia, treatment order.
Have the authors identified all important confounding factors?	Yes	Small, short-term, feasibility study; larger study with long-term follow-up is needed.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	Single-arm study with no control group
Was the follow-up of patients complete?	Yes	Data were reported for 24 out 25 patients enrolled.
How precise (for example, in terms of confidence interval and p values) are the results?		95% CIs not reported. However, P-values (P<0.001 for back and leg pain) indicate statistically significant pre vs post HF10 differences.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.		

Abbreviations: N/A, not applicable.
Source: Tiede et al. (2013) (29).

Table 20: Quality assessment, Rapcan et al. (2015)

Study name	**Rapcan et al. (2015) (24)**	
Study question	**Response (yes/no/not clear/NA)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Patients with FBSS treated with HF10™ therapy at 4 Slovakian centres.
Was the exposure accurately measured to minimise bias?	Yes	Patients underwent 7-14 day trials with HF10™ therapy to assess efficacy, those with at ≥50% reduction in pain proceeded to permanent implant.
Was the outcome accurately measured to minimise bias?	Yes	Outcomes included visual analogue scale (VAS), patient satisfaction, patient performance status, opioid use, and complication rate.
Have the authors identified all important confounding factors?	No	The authors only mention the absence of blinding as a confounding factor.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	Single-arm study with no control group
Was the follow-up of patients complete?	Yes	Data reported through 12 months for all 21 patients.
How precise (for example, in terms of confidence interval and p values) are the results?		Mean difference in VAS pain score before versus 12 months after post implantation = 4.7 (95% CI: 3.9 to 5.4, P< 0.001). Mean difference in performance status before versus 12 months after post implantation = 1.2 (95% CI: 0.9 to 1.6, P< 0.001).
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.		

Abbreviations: CI, confidence interval; FBSS, failed back surgery syndrome; N/A not applicable.
Source: Rapcan et al. (2015) (24).

Table 21: Quality assessment, Al-Kaisy et al. (2016)

Study name	Al-Kaisy et al. (2016) (25)	
Study question	**Response (yes/no/not clear/NA)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients with chronic axial low back pain with no prior history of spinal surgery (and not suitable candidates for future spinal surgery) were recruited at a single centre in UK with ethical committee approval.
Was the exposure accurately measured to minimise bias?	Yes	Patients underwent a 7-10 day trial with HF10™ therapy to assess efficacy; those with ≥50% reduction in pain proceeded to permanent implant.
Was the outcome accurately measured to minimise bias?	Yes	Outcome measures included the visual analogue scale (VAS), Oswestry Disability Index (ODI), HRQoL, opioid use.
Have the authors identified all important confounding factors?	Yes	Single site, small sample size, no control group.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	Single-arm study with no control group
Was the follow-up of patients complete?	Yes	Data are reported for all patients.
How precise (for example, in terms of confidence interval and p values) are the results?		95% confidence intervals not reported. However, P-values (P,0.05 to P<0.0001 for leg and back pain and functional score) indicate statistically significant pre versus post HF10™ differences.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.		

Abbreviations: HRQoL, health-related quality of life; N/A, not applicable.
Source: Al-Kaisy et al. (2016) (25).

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in Table 22.

In this section results are presented for each relevant study listed in Table 6. Where applicable, outcomes are split into two separate tables; 1) pain outcomes and 2) other outcomes including HRQoL, physical functioning, opioid use, and patient satisfaction.

Reason for explant removal is a specified outcome in the final scope and is provided from the SENZA-RCT in Table 24. This data is unpublished and highlighted as commercial in confidence.

In section 7.6.3, unpublished patient satisfaction data is also provided from a survey among 2,977 patients at 2, 5 and 11 months post permanent implantation with HF10™ therapy.

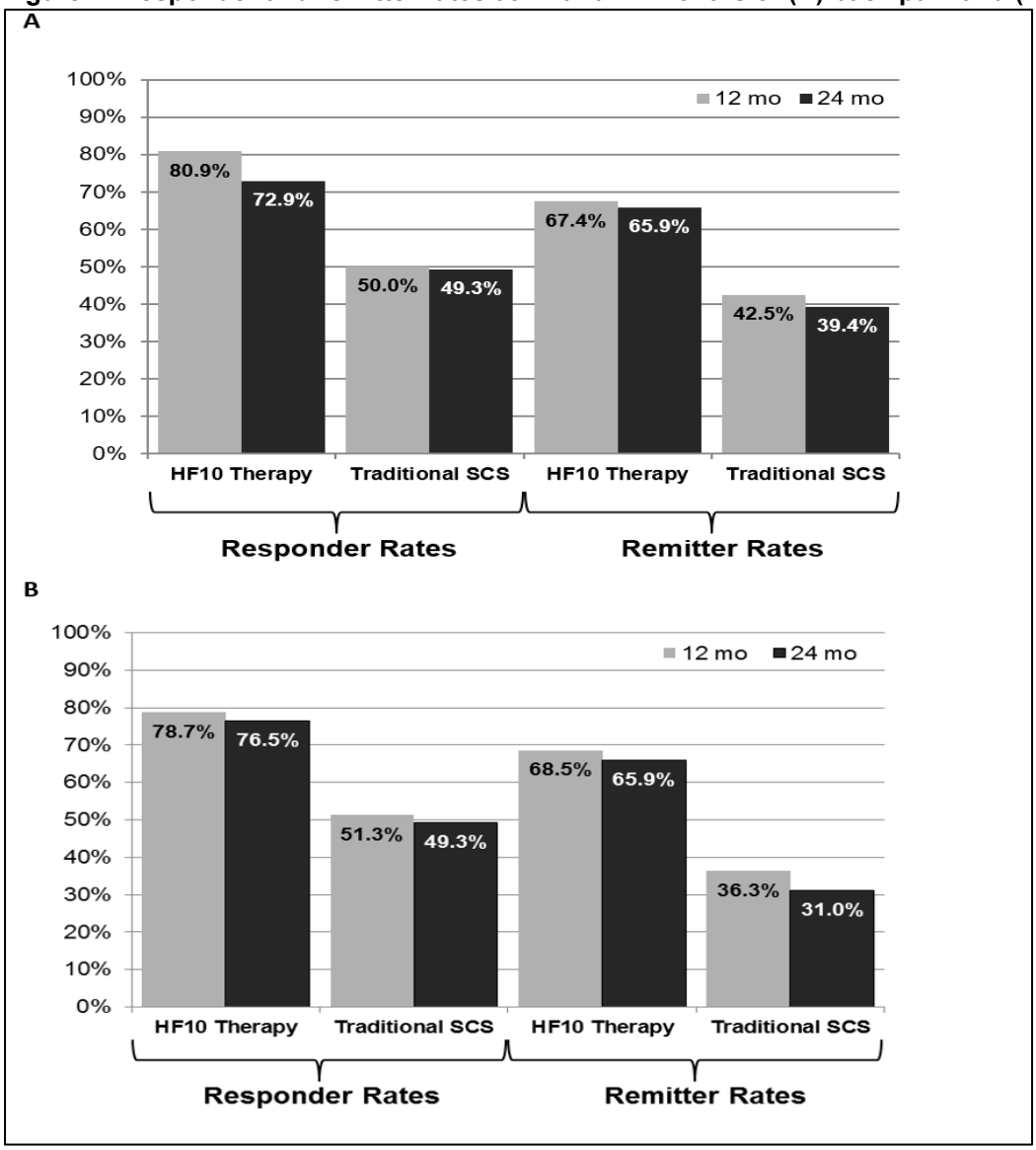
Table 22: Results from the SENZA-RCT - pain outcomes (Kapural et al. 2015 and Kapural et al. 2016)

Outcome/ Timepoint	HF10™ therapy	Traditional low-frequency SCS	P value	Comments
Patients who respond to SCS therapy for back pain (≥50% reduction in VAS score) without a stimulation-related neurological deficit, % (see also supplementary Figure 7)				
Month 3 (primary outcome)	84.5 n=90	43.8 n=81	<0.001†	
Month 6	76.4 n=90	51.9 n=81	N/R	
Month 12	78.7 n=90	51.3 n=81	N/R	
Month 24	76.5 n=85	49.3 n=71	<0.001†	27.2 difference, 95% CI: 10.1 to 41.8
Patients who respond to SCS therapy for leg pain (≥50% reduction in VAS score) without a stimulation-related neurological deficit, % (see also supplementary Figure 7)				
Month 3	83.1 n=90	55.0 n=81	<0.001†	
Month 6	80.9 n=90	54.4 n=81	N/R	
Month 12	78.7 n=90	51.3 n=81	N/R	
Month 24	72.9 n=85	49.3 n=71	<0.001 (non-inferiority), =0.003 (superiority)	23.6 difference, 95% CI: 5.9 to 38.6
Patients classified as remitters for back pain (VAS score of ≤2.5 cm), % (see also supplementary Figure 7)				
Month 24	65.9 n=85	31.0 n=71	<0.001 (non-inferiority), =0.003 (superiority)	34.9 difference, 95% CI: 18.0 to 49.0
Patients classified as remitters for leg pain (VAS score of ≤2.5 cm), % (see also supplementary Figure 7)				
Month 24	65.9 n=85	39.4 n=71	<0.001 (non-inferiority), =0.001 (superiority)	26.5 difference, 95% CI: 8.0 to 41.2
Mean back VAS pain score (see also supplementary Figure 8 and Figure 9)				
Baseline (SD)	7.4 (1.2) n=89	7.8 (1.2) n=80		
Month 24 (SD)	2.4 (2.3) n=85	4.5 (2.9) n=71	<0.001 for non-inferiority and superiority (absolute change treatment difference -1.7) <0.001 for non-inferiority and superiority (relative	Absolute change HF10™ therapy; -5.0 (2.5) Absolute change traditional low-frequency; -3.2 (3.0) Relative change HF10™ therapy; --66.9 (31.8)

			change treatment difference -25.8)	Relative change traditional low-frequency; -41.1 (36.8)
Mean leg VAS pain score (see also supplementary Figure 8 and Figure 9)				
Baseline (SD)	7.1 (1.5) n=89	7.6 (1.4) n=80		
Month 24 (SD)	2.4 (2.5) n=85	3.9 (2.8) n=71	<0.001 for non-inferiority and =0.03 for superiority (absolute change treatment difference -1.0) <0.001 for non-inferiority and =0.002 for superiority (relative change treatment difference -19.1)	Absolute change HF10™ therapy; -4.7 (2.8) Absolute change traditional low-frequency; -3.7 (3.0) Relative change HF10™ therapy; -65.1 (36.0) Relative change traditional low-frequency; -46.0 (40.4)

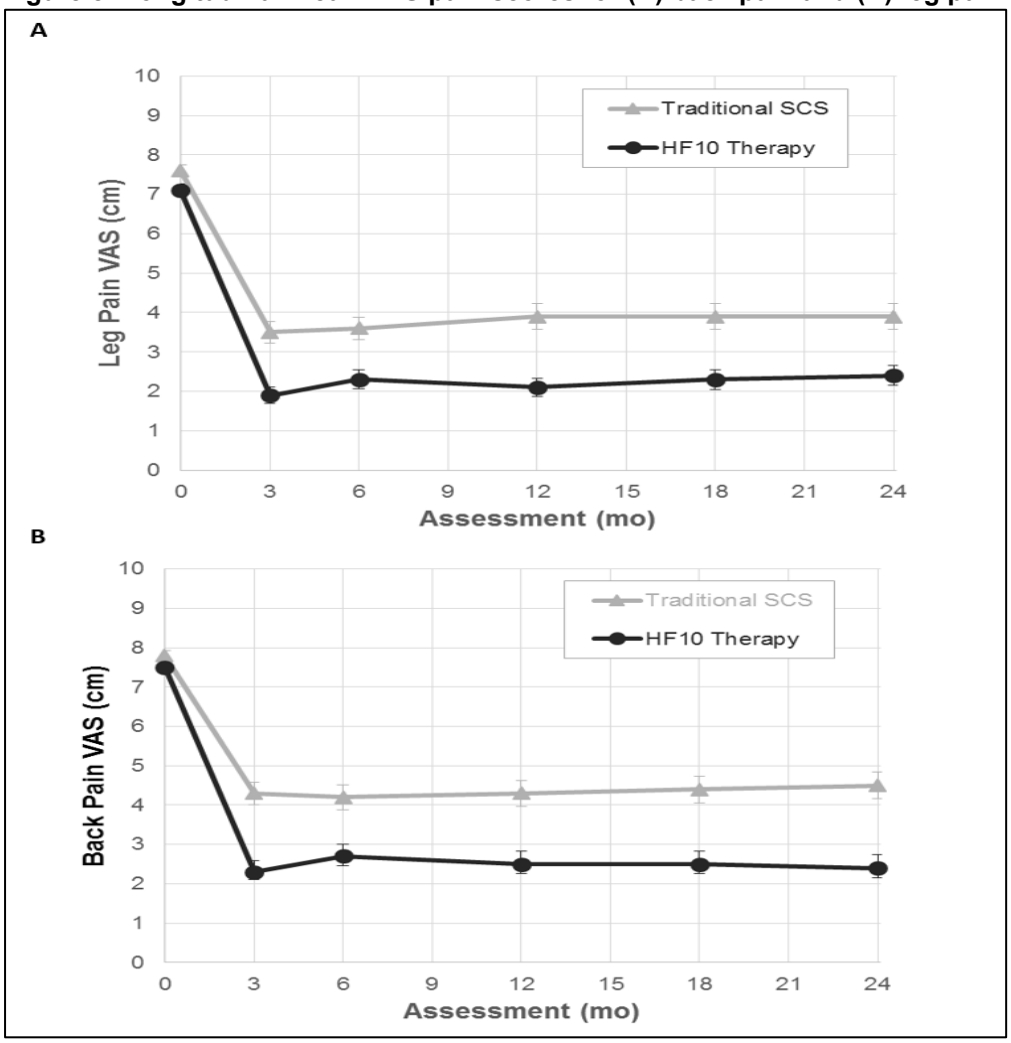
Abbreviations: CI, confidence interval; N/R, not reported; VAS, visual analogue scale
† For both non-inferiority and superiority.
Source: Kapural et al. (2015) and Kapural et al. (2016) (19, 20).

Figure 7: Responder and remitter rates at 12 and 24 months or (A) back pain and (B) leg pain



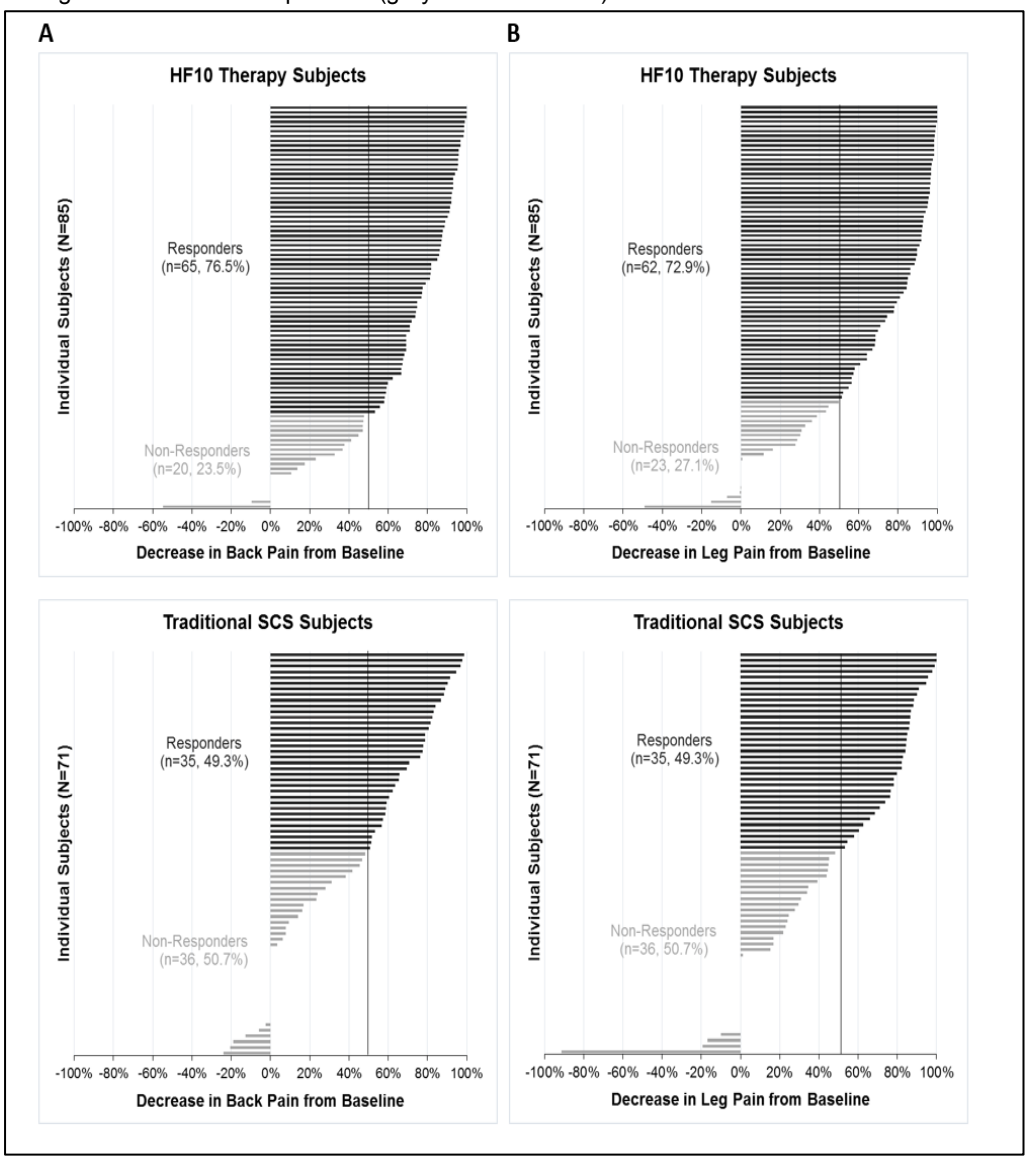
Abbreviations: Mo, months; SCS, spinal cord stimulation.
Source: Kapural et al. (2016) (20).

Figure 8: Longitudinal mean VAS pain scores for (A) back pain and (B) leg pain



Abbreviations: Mo, months; SCS, spinal cord stimulation; VAS, visual analogue scale.
Source: Kapural et al. (2016) (20).

Figure 9: Individual patient responses at 24 months for (A) back pain and (B) leg pain
Each horizontal line represents the response of a patient. Responders (coloured horizontal lines), are distinguished from non-responders (grey horizontal lines).



Abbreviations: SCS, spinal cord stimulation.
Source: Kapural et al. (2016) (20).

Table 23: Results from the SENZA-RCT - other outcomes (Kapural et al. 2015, Kapural et al. 2016 and Amirdelfan et al. 2016)

Outcome/ Timepoint	HF10™ therapy	Traditional low-frequency SCS	P value	Comments
Distribution of ODI categorisation, %				
Baseline	n=85	n=71	=0.41	
Minimal	0.0	0.0		
Moderate	9.4	1.4		
Severe	69.4	77.5		
Crippled	21.2	21.1		
Month 24	n=85	n=71	=0.02	
Minimal	23.5	9.9		
Moderate	41.2	39.4		
Severe	30.6	42.3		
Crippled	4.7	8.5		
PGIC categorisation, %				
Month 24	n=85	n=71	=0.004 between groups	
A great deal better	34.1	21.1		
Better	29.4	15.5		
Moderately better	11.8	19.7		
Somewhat better	4.7	12.7		
A little better	2.4	5.6		
Almost the same	8.2	4.2		
No change	9.4	21.1		
CGIC categorisation, %				
Month 24	n=85	n=71	=0.002 between groups	
A great deal better	40.7	20.0		
Better	27.9	28.6		
Moderately better	9.3	12.9		
Somewhat better	8.1	12.9		
A little better	2.3	1.4		
Almost the same	1.2	1.4		
No change	10.5	22.9		
GAF (transient, minimal or no symptoms), %				
Baseline	24.7	30.0	N/R	
Month 12	70.8	60.8	N/R	
Mean improvement in GAF scores (SE)				
Month 12	13.8 (± 1.3)	7.9 (± 1.3)	<0.01	
Sleeping and driving with device turned on, %				
Month 12	n=86	n=69	<0.001	

Sleeping	95.3	59.4		
Month 12 Driving	n=86 93.8	n=69 65.5	<0.001	
Patient satisfaction, %				
Month 24 Very satisfied Satisfied Not sure Dissatisfied Very dissatisfied	n=85 60.0 26.3 10.0 1.3 0.0	n=71 40.4 45.6 10.5 3.5 0.0	=0.07 between groups	
Charging satisfaction, % of patients answering, 'very satisfied' or 'satisfied'				
Convenience of charging device	87.3	70.0	0.036	
How often do you need to charge your device?	94.5	80.0	0.048	
Length of time needed to charge your device	80.0	72.5	0.463	
How easy is it to charge your device?	81.8	70.0	0.221	
How well charging your device fits into your schedule?	90.9	72.5	0.026	
Patient reliance on remote control, %				
Use of remote control to adjust therapy settings	74.5	87.5		
Frequency of adjusting therapy settings (% once per day or more often presented)	0.0	40.5		HF10™ therapy patients did not need to adjust settings daily
Conclusion: This study demonstrates long-term superiority compared with traditional low-frequency SCS in treating both leg and back pain. HF10™ therapy resulted in sustained improvement in HRQoL measures that are statistically significant and clinically meaningful. The advantages of HF10™ therapy are anticipated to impact the management of chronic pain patients substantially.				

Abbreviations: CGIC, clinician global impression of change; Global assessment of functioning; HRQoL, health-related quality of life; N/R, not reported; ODI, Oswestry disability index; PGIC, patient global impression of change; SCS, spinal cord stimulation; SE, standard error.

† For both non-inferiority and superiority.

Source: Kapural et al. (2015), Kapural et al. (2016) (19, 20) and Amirdelfan et al. (2016) (30).

Table 24: Reason for explant removal in the SENZA-RCT (unpublished data – Contains AiC)

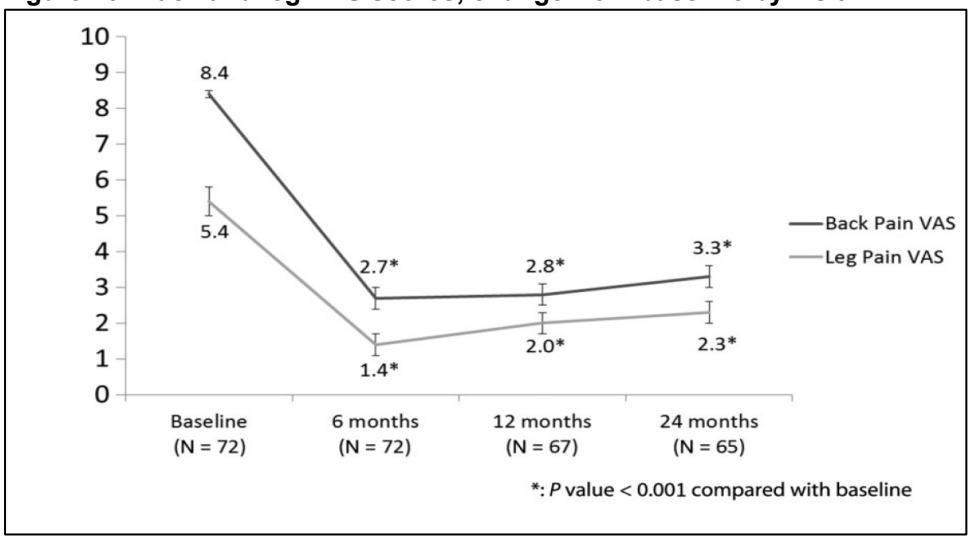
	HF10™ therapy		Traditional low-frequency SCS	
	N	**%**	**N**	**%**
Subjects implanted	90		81	
Subjects implanted at end of year 1	[redacted]	[redacted]	[redacted]	[redacted]
Subjects explanted in year 1	[redacted]	[redacted]	[redacted]	[redacted]
Explanted due to poor efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Explanted due to paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Explanted due to other AE	[redacted]	[redacted]	[redacted]	[redacted]
Subjects implanted at end of year 2	[redacted]	[redacted]	[redacted]	[redacted]
Subjects explanted in year 2*	[redacted]	[redacted]	[redacted]	[redacted]
Explanted due to poor efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Explanted due to other AE	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Table 25: Results from the SENZA-EU study - pain outcomes (Van Buyten et al. 2013 and Al-Kaisy et al. 2014)

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean back VAS pain score (see also supplementary Figure 10)			
Baseline (SE)	8.4 (± 0.1) n=72	<0.001 (24 months compared with baseline)	At 24 months, 60% of implanted patients had a least 50% back pain relief
24 months (SE)	3.3 (± 0.3) n=65		
Mean leg VAS leg score (see also supplementary Figure 10)			
Baseline (SE)	5.4 (± 0.4) n=72	<0.001 (24 months compared with baseline)	At 24 months, 71% of implanted patients had a least 50% leg pain relief
24 months (SE)	2.3 (± 0.3) n=65		

Abbreviations: SE, standard error; VAS, visual analogue scale.
Source: Al-Kaisy et al. (2014) (23).

Figure 10: Back and leg VAS scores, change from baseline by visit



Abbreviations: VAS, visual analogue scale.
Source: Al-Kaisy et al. (2014) (23).

Table 26: Results from the SENZA-EU, subgroup analyses (Van Buyten et al. 2013 and Al-Kaisy et al. 2014)

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean back VAS pain score in patients with FBSS			
Baseline (SE)	8.5 (± 0.2) n=67	<0.001 (24 months compared with baseline)	
24 months (SE)	3.2 (± 0.4) n=67		
Mean leg VAS pain score in patients with FBSS			
Baseline (SE)	5.3 (± 0.4) n=67	<0.001 (24 months compared with baseline)	
24 months (SE)	2.1 (± 0.3) n=67		
Mean back VAS pain score in patients without prior back surgery			
Baseline (SE)	8.1 (± 0.2) n=15	<0.001 (24 months compared with baseline)	The positive results in this group of patients indicate that HF10™ therapy may be an effective treatment for patients in whom back surgery is not indicated
24 months (SE)	3.4 (± 0.7) n=15		
Mean leg VAS pain score in patients without prior back surgery			
Baseline (SE)	5.9 (± 0.8) n=15	<0.05 (24 months compared with baseline)	
24 months (SE)	2.8 (± 0.7) n=15		
Mean back VAS pain score in patients who have previously failed traditional low-frequency SCS			

Baseline (SE)	8.9 (± 0.3) n=11	<0.05 (24 months compared with baseline)	
24 months (SE)	4.2 (± 0.9) n=11		
Mean leg VAS pain score in patients who have previously failed traditional low-frequency SCS			
Baseline (SE)	7.7 (± 0.8) n=11	<0.05 (24 months compared with baseline)	
24 months (SE)	2.5 (± 0.6) n=11		

Abbreviations: SE, standard error; visual analogue scale.
Source: Al-Kaisy et al. (2014) (23).

Table 27: Results from the SENZA-EU study - other outcomes (Van Buyten et al. 2013 and Al-Kaisy et al. 2014)

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean ODI score			
Baseline (SE)	55 (± 1.0) n=72	<0.001 (24 months compared with baseline)	90% of patients were classified as crippled or severely disabled at baseline, and this reduced to 49% at 24 months
24 months (SE)	40 (± 2.0) n=65		
Mean subjective sleep disturbances per night			
Baseline (SD)	3.7 (± 0.4) n=72	<0.001 (24 months compared with baseline)	
24 months (SD)	1.4 (± 0.2) n=65		
Patients taking opioids, %			
Baseline	86 n=72	<0.001 (24 months compared with baseline)	
24 months	57 n=65		
Mean dose of oral morphine, mg/day			
Baseline	84 n=72	<0.001 (24 months compared with baseline)	
24 months	27 n=65		
Satisfied or very satisfied with HF10™ therapy (based on a 5-point scale), %			
Month 24	85 n=N/R	-	
Recommend or highly recommend to others, %			
Month 24	88 n=N/R	-	
Conclusion: In patients with chronic back pain with or without leg pain, HF10™ therapy resulted in clinically significant and sustained back and leg pain relief, functional and sleep improvements, opioid reduction, and high patient satisfaction.			

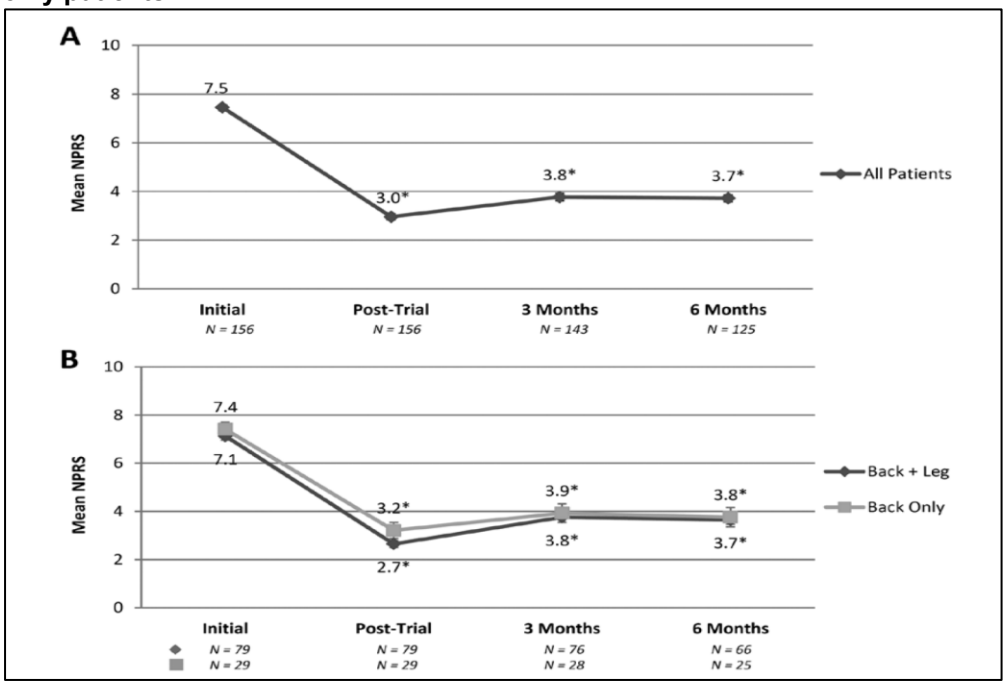
Abbreviations: SD, standard deviation; SE, standard error; N/R, not reported.
Source: Al-Kaisy et al. (2014) (23).

Table 28: Results from Russo et al. (2016)† - pain outcomes

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean overall pain (NPRS) scores (all patients) (see also supplementary Figure 11)			
Initial	7.5 n=156		Approximately 50% reduction from baseline at 3 and 6 months post-implant
Post-trial phase	3.0 n=156	<0.001	
3 months	3.8 n=143	<0.001	
6 months	3.7 n=125	<0.001	
Mean overall pain (NPRS) scores (back only patients) (see also supplementary Figure 11)			
Initial	7.4 n=29		Approximately 50% reduction from baseline at 3 and 6 months post-implant
Post-trial phase	3.2 n=29	<0.001	
3 months	3.9 n=28	<0.001	
6 months	3.8 n=25	<0.001	
Mean overall pain (NPRS) scores (back and leg patients) (see also supplementary Figure 11)			
Initial	7.1 n=79	-	Success rate 81%. Patients with back and concomitant leg pain demonstrated the highest success rate.
Post-trial phase	2.7 n=79	<0.001	
3 months	3.8 n=76	<0.001	
6 months	3.7 n=66	<0.001	
Mean overall pain (NPRS) scores (patients who had previously failed traditional low-frequency SCS/PNFS) (see also supplementary Figure 12)			
Initial	7.2 n=47	-	At 6 months post-implant, 55% of previously failed stimulator patients reported 50% pain reduction and 8% reported ≥80% pain reduction (n=38).
Post-trial phase	3.2 n=47	<0.001	
3 months	4.0 n=42	<0.001	
6 months	3.7 n=38	<0.001	

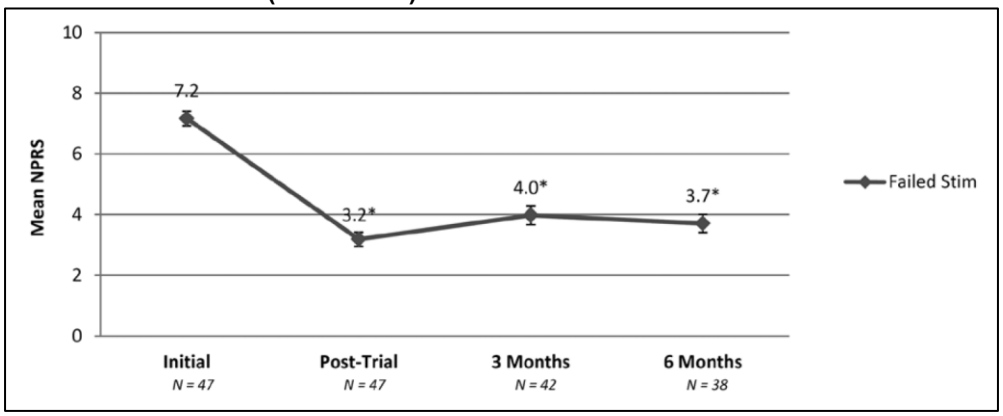
Abbreviations: NPRS, numerical pain rating scale; PNFS, peripheral nerve field stimulation; SCS; spinal cord stimulation.
† Results are presented for the patient population of relevance to this submission.
Source: Russo et al. (2016) (28).

Figure 11: Mean overall pain (NPRS) scores for (A) all patients and (B) back and leg and back only patients



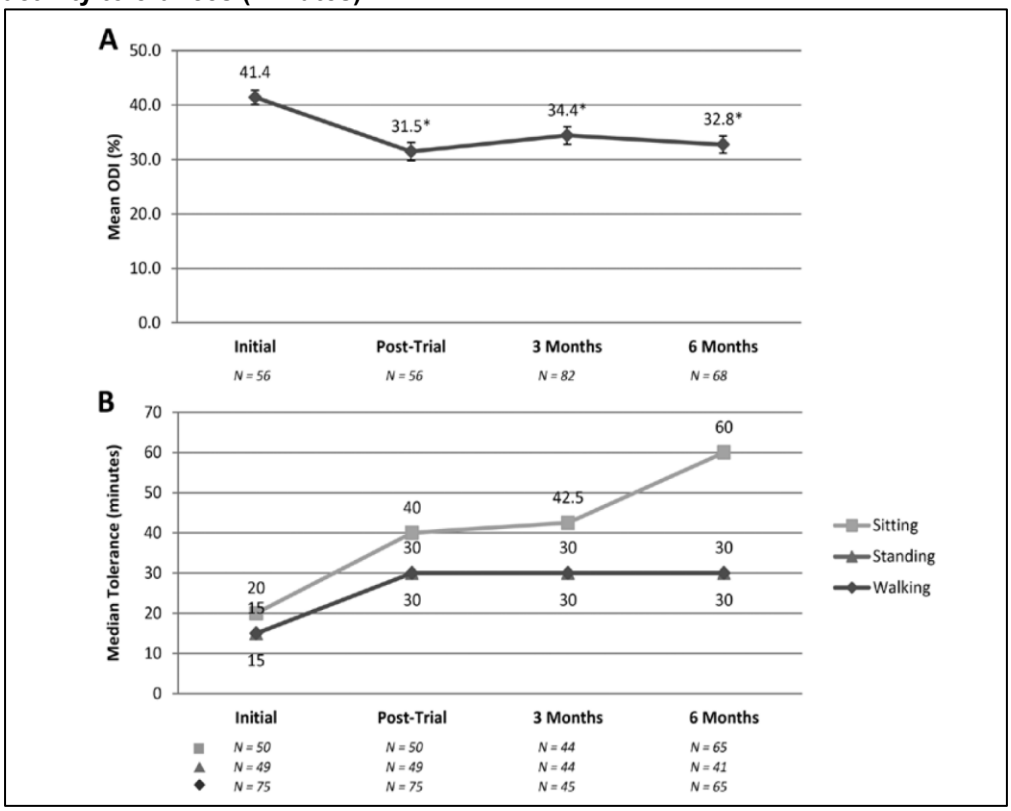
Abbreviations: NPRS, numerical pain rating scale.
* p<0.001.
Source: Russo et al. (2016) (28).

Figure 12: Mean overall pain (NPRS) scores for patients who had previously failed traditional stimulator treatment (SCS/PNFS)



Abbreviations: PNFS, peripheral nerve field stimulation; NPRS, numerical pain rating scale; spinal cord stimulation; stim, stimulation.
* p<0.001.
Source: Russo et al. (2016) (28).

Figure 13: Functional outcome results for all patients for (A) mean ODI (%) and (B) median activity tolerances (minutes)



Abbreviations: ODI, Oswestry disability index.
* p<0.001.
Source: Russo et al. (2016) (28).

Table 29: Results from Russo et al. (2016)† - other outcomes

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean ODI (all patients), % (see also supplementary Figure 13)			
Initial	41.4 n=56	-	
Post-trial phase	31.5 n=56	<0.001	
3 months	34.4 n=82	<0.001	A mean 7-point reduction in ODI was observed at 3 months post-implant
6 months	32.8 n=68	<0.001	A mean 8.6-point reduction (21%) in ODI was observed at 6 months post-implant. This was significantly correlated to NPRS at 6 months (r = 0.503, p <0.001).
Median activity tolerances, minutes (see also supplementary Figure 13)			
Initial			

Sitting Standing Walking	20 n=50 15 n=49 15 n=75		
Post-trial phase Sitting Standing Walking	 40 n=50 30 n=49 30 n=75	 - - -	
3 months Sitting Standing Walking	 42.5 n=44 30 n=44 30 n=45	 - - -	
6 months Sitting Standing Walking	 60 n=65 30 n=41 30 n=65	 - - -	Median sitting tolerance was improved by 40 minutes and median standing and walking tolerances were improved by 15 minutes at 6 months. NPRS was also significantly negatively correlated to standing (r = -0.261, p<0.05) at 6 months post-implant.
Conclusion: These retrospective results demonstrate a significant advancement for patients with chronic pain and are consistent with published clinical results from other studies of HF10™ therapy. HF10™ therapy appears to be a viable, paraesthesia-free alternative to traditional low-frequency SCS, with high trial success rates. HF10™ therapy demonstrated effectiveness in a range of pain distributions including those difficult to treat with traditional SCS, and the possibility to restore pain control in patients who have previously failed traditional SCS.			

Abbreviations: NPRS, numerical pain rating scale; Oswestry disability index; SCS; spinal cord stimulation.
† Results are presented for the patient population of relevance to this submission.
Source: Russo et al. (2016) (28).

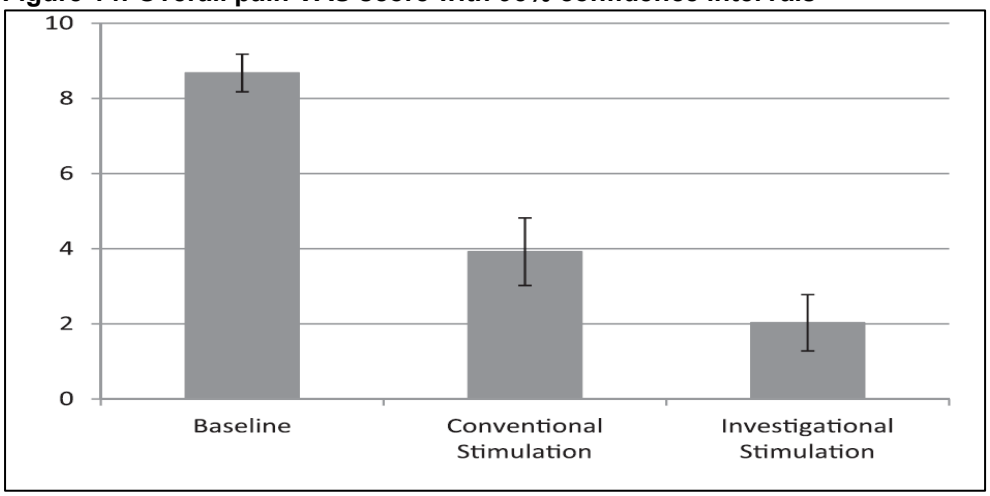
Table 30: Results from Tiede et al. (2013) - pain outcomes

Outcome/Timepoint	HF10™ therapy	Traditional low-frequency SCS	P value	Comments
Mean VAS pain score (overall pain) (see also supplementary Figure 14)				
Overall VAS baseline (HF10™ therapy and traditional low-frequency SCS)	8.68 95% CI: ± 0.50 n=24			

VAS at conclusion of traditional low-frequency SCS	-	3.92 95% CI: ± 0.90 n=24	<0.001	55% reduction from baseline
VAS at conclusion of HF10™ therapy	2.03 95% CI: ± 0.75 n=24	-	<0.001	77% reduction from baseline
Mean VAS pain score (back pain) (see also supplementary Figure 15)				
Back VAS baseline (HF10™ therapy and traditional low-frequency SCS)	8.12 95% CI: ± 0.93 n=18			
VAS at conclusion of traditional low-frequency SCS		N/R		
VAS at conclusion of HF10™ therapy	1.88 95% CI: ± 0.85 n=18	<0.001		77% reduction from baseline

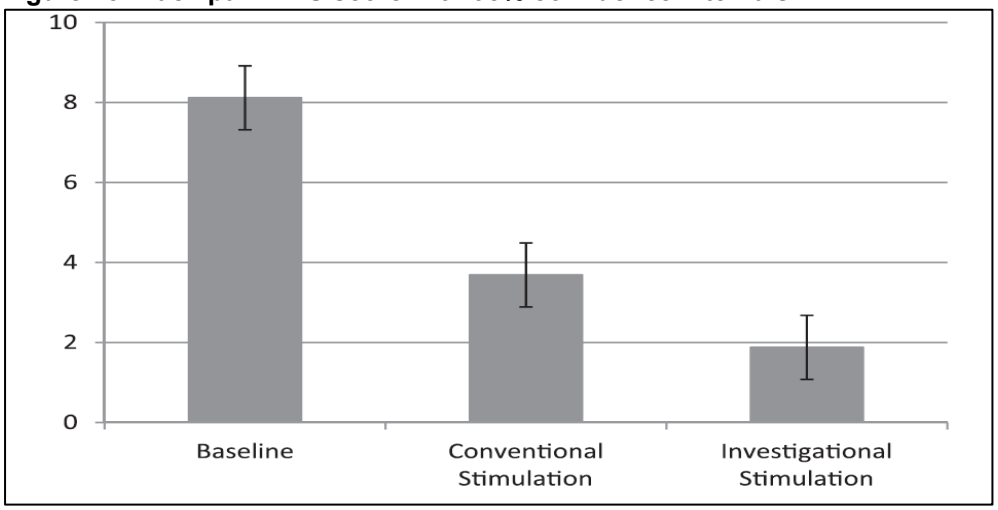
Abbreviations: CI, confidence interval; N/R, not reported; SCS; spinal cord stimulation; VAS, visual analogue scale.
Source: Tiede et al. (2013) (29).

Figure 14: Overall pain VAS score with 95% confidence intervals



Conventional = traditional low-frequency SCS, investigational = HF10™ therapy.
Source: Tiede et al. (2013) (29).

Figure 15: Back pain VAS score with 95% confidence intervals



Conventional = traditional low-frequency SCS, investigational = HF10™ therapy.
Source: Tiede et al. (2013) (29).

Table 31: Results from Tiede et al. (2013) – other outcomes

Outcome/Timepoint	HF10™ therapy	Traditional low-frequency SCS	P value	Comments
Patient preference, %				
	88	12	HF10™ therapy was preferred to traditional low-frequency SCS (21/24 patients, 88%)	
Conclusion: Patients with predominant back pain reported a substantial reduction in overall pain and back pain when treated with HF10™ therapy.				

Abbreviations: SCS; spinal cord stimulation.
Source: Tiede et al. (2013) (29).

Table 32: Results from Rapcan et al. (2015) - pain outcomes

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean back and leg VAS pain score (SD)			
Before implantation	8.7 (± 0.88)		
Immediately after implantation	3.9 (± 1.13) 95% CI: 4.2 to 5.5	<0.001	
3 months	4.4 (± 1.4) 95% CI: 3.6 to 5.1	<0.001	
6 months	4.4 (± 1.5) 95% CI: 3.6 to 5.1	<0.001	
9 months	4.0 (± 1.5) 95% CI: 4.0 to 5.5	<0.001	
12 months	4.0 (± 1.5) 95% CI: 3.9 to 5.4	<0.001	At 12 months, 67% of patients still met the 50% pre-implant pain reduction criterion

Abbreviations: CI, confidence interval; SD, standard deviation; VAS, visual analogue scale.
Source: Rapcan et al. (2015) (24).

Table 33: Results from Rapcan et al. (2015) - other outcomes

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean performance status (SD) (see also supplementary Table 34)			
Before implantation	3.0 (± 0.38)		
Immediately after implantation	2.0 (± 0.6) 95% CI: 0.6 to 1.3	<0.001	
3 months	1.95 (± 0.6) 95% CI: 0.8 to 1.4	<0.001	
6 months	1.95 (± 0.6) 95% CI: 0.8 to 1.4	<0.001	
9 months	1.95 (± 0.5) 95% CI: 0.8 to 1.4	<0.001	
12 months	1.8 (± 0.6) 95% CI: 0.9 to 1.6	<0.001	
Mean patient satisfaction scores (SD)			
Immediately after implantation	6.9 (± 3.5)	-	The mean patient satisfaction scores did not differ through 12 months follow-up
12 months	6.8 (± 2.9)	-	
Opioid use			
	After 12 months, 65% of patients had their opioid use reduced by a half	-	
Conclusion: Patients implanted with HF10™ therapy reported significant leg and back pain relief within the period of 12 months as well as significant improvement in their performance status.			

Abbreviations: CI, confidence interval; SD, standard deviation.
Source: Rapcan et al. (2015) (24).

Table 34: Supplementary table, performance status change, Rapcan et al. (2016)

Number of patients	Before implant	6 months	12 months
No symptoms, normal life	0	0	0
Able to carry out normal activities, part-time employment	0	4	6
Unable to work, able to care for personal needs	1	14	13
Limited in care for oneself	18	3	2
Unable to care for oneself, confined to bed	2	0	0

Source: Rapcan et al. (2015) (24).

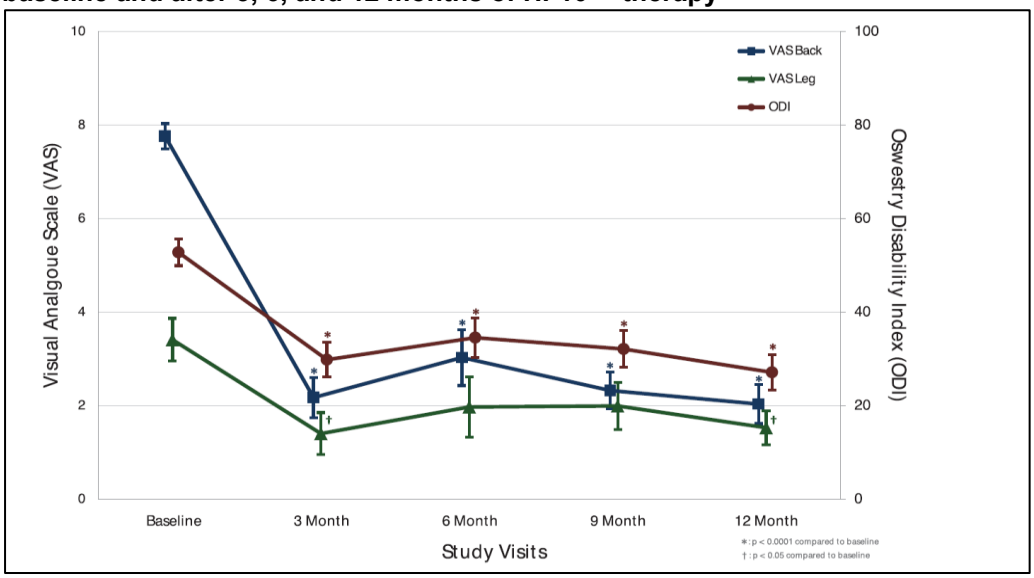
Table 35: Results from Al-Kaisy et al. (2016)

Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean back VAS pain score (see also supplementary Figure 16)			

Baseline (SD)	7.9 (± 1.3) n=N/R		59.9% and 72.6% reduction versus baseline at 6 and 12 months, respectively. 75% and 90% of implanted patients were classified as responders (VAS reduction >50%) at 6 and 12 months, respectively.
Reduction at 6 months (SD)	4.69 (± 2.78) n=N/R	<0.0001	
Reduction at 12 months (SD)	5.59 (± 1.80) n=N/R	<0.0001	
Mean back VAS leg score (see also supplementary Figure 16)			
Baseline (SD)	3.3 (± 2.1) n=N/R		
Reduction at 6 months (SD)	Exact data N/R	<0.05	
Reduction at 12 months (SD)	Exact data N/R	<0.05	

Abbreviations: N/R, not reported; SD, standard deviation; VAS, visual analogue scale.
Source: Al-Kaisy et al. (2016) (25).

Figure 16: Pain (VAS scores for both back and leg) and physical disability (ODI score) at baseline and after 3, 6, and 12 months of HF10™ therapy



Abbreviations: ODI, Oswestry disability index; VAS, visual analogue scale.
Source: Al-Kaisy et al. (2016) (25).

Table 36: Results from Al-Kaisy et al. (2016) - other outcomes

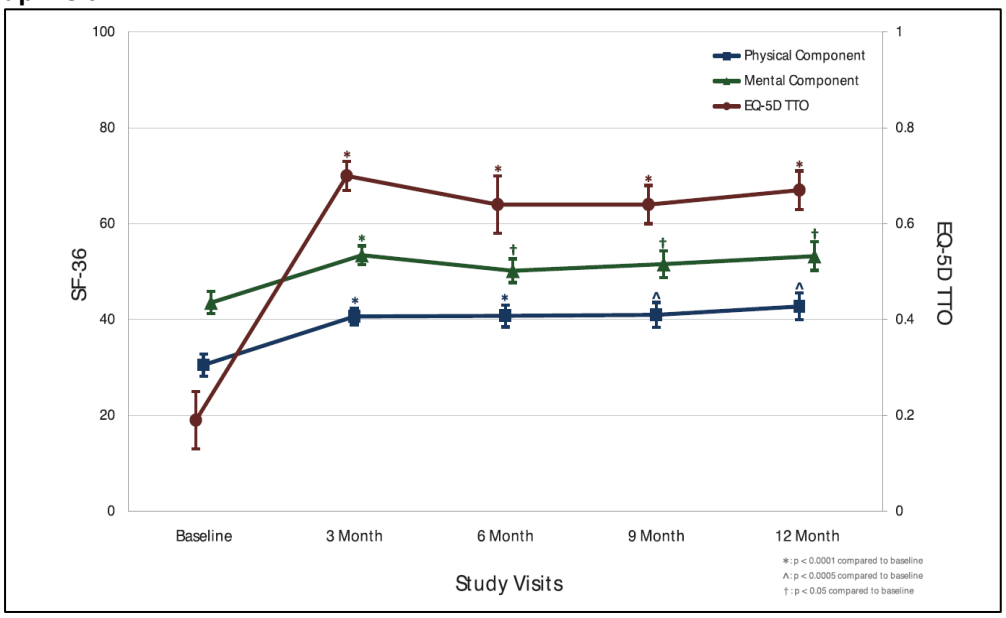
Outcome/Timepoint	HF10™ therapy	P value	Comments
Mean ODI score (see also supplementary Figure 16)			
Baseline (SD)	53.0 (± 13.0) n=N/R		33.2% and 47.6% reduction versus baseline at 6 and
Reduction at 6 months (SD)	18.40 (± 20.15) n=N/R	<0.0001	

Reduction at 12 months (SD)	26.00 (± 19.05) n=N/R	<0.0001	12 months, respectively. At 12 months, 9 patients (45%) were in the "minimal disability" category, a 20% improvement versus baseline, 5 patients (25%).
Mean subjective sleep disturbances per night			
Baseline (SD)	Exact data N/R		37% and 54% reduction versus baseline at 6 and 12 months, respectively
Reduction at 6 months (SD)	Exact data N/R	<0.05	
Reduction at 12 months (SD)	Exact data N/R	<0.05	
Mean sleep duration per night, hours			
Baseline (SD)	Exact data N/R		22% and 24% increase versus baseline at 6 and 12 months, respectively
Increase at 6 months (SD)	1.00 (± 1.45) n=N/R	=0.074	
Increase at 12 months (SD)	1.15 (± 1.42) n=N/R	=0.062	
Mean dose of oral morphine, mg/day			
Baseline (SD)	112.0 (± 87.0) n=N/R	=0.0833 (Unclear as to whether this p-value relates to daily opioid intake at month 12 or the three patients which ceased opioid medication completely)	64% (72 mg/day) reduction versus baseline at 12 months
12 months (SD)	40.0 (± 13.0) n=N/R		
Mean EQ-5D TTO score (see also supplementary Figure 17)			
Baseline (SD)	0.17 (± 0.28) n=N/R		0.47 QALY gain at 12 months
12 months (SD)	Exact data N/R	<0.0001	
SF-36 physical component score (see also supplementary Figure 17)			
Baseline (SD)	30.3 (± 8.1) n=N/R		
12 months (SD)	Exact data N/R	<0.0005	
SF-36 mental component score (see also supplementary Figure 17)			
Baseline (SD)	42.7 (± 11.2) n=N/R		
12 months (SD)	Exact data N/R	<0.05	
No. employed			
Baseline	11 n=19		
12 months	15 N=19	=0.0833	
Satisfied with HF10™ therapy, %			

12 months	90 n=N/R	-	
Recommend HF10™ therapy to others, %			
12 months	100 n=N/R	-	70% of patients would highly recommend HF10™ therapy to others
Conclusion: HF10™ therapy may provide significant leg and back pain relief, reduction in disability, improvement in HRQoL, and reduction in opioid use in patients with no history of spinal surgery.			

Abbreviations: EQ-5D, EuroQol 5-dimension; HRQoL, health-related quality of life; mg, milligram; N/R, not reported; ODI, Oswestry disability index; SD, standard deviation; SF-36, short-form 36; TTO, time trade-off; VAS, visual analogue scale.
Source: Al-Kaisy et al. (2016) (25).

Figure 17: HRQoL measurements (EQ-5D and SF-36) at baseline and at each scheduled follow-up visit



Abbreviations: EQ-5D, EuroQol 5-dimension; SF-36, short-form 36; TTO, time trade-off.
Source: Al-Kaisy et al. (2016) (25).

Table 37: Results from De Carolis et al. (2017)†

Outcome	HF10™ therapy	P value	Comments
Mean VAS pain score (SD)			
Prior to HF10™ therapy	7.8 (± 1.3)		
At time of testing after HF10™ therapy	2.5 (± 2.1)	N/R	70.0% (± 24.0) average pain relief

Abbreviations: N/R, not reported; SD, standard deviation; VAS, visual analogue scale.
† Results are presented for non-technical outcomes only.
Source: De Carolis et al. (2017) (26).

7.6.2 Justify the inclusion of outcomes in Table 22 from any analyses other than intention-to-treat.

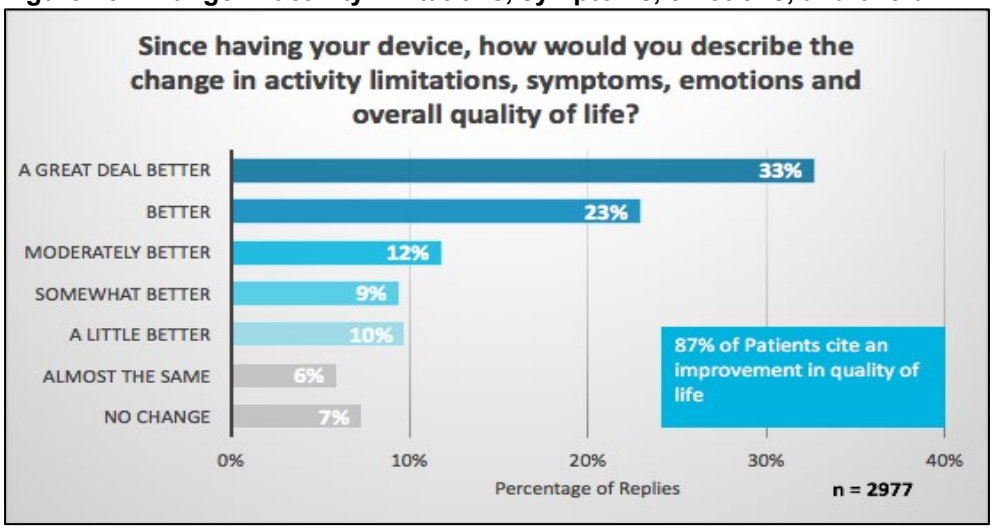
No analyses other than intention-to-treat (ITT) were conducted.

7.6.3 Long-term US patient satisfaction feedback (~2,977 patients)

Nevro Corporation actively tracks performance measures to continuously improve patient outcomes. Data is collected by the Nevro Therapy Support Specialist (TSS) team, which was uniquely created to track and optimise long-term outcomes. Patients are asked for feedback via telephone at major therapy milestones. The results below represent recent feedback from among 2,977 patients at 2, 5, and 11 months post permanent implantation with HF10™ therapy (the latest result from each patient is included) (31):

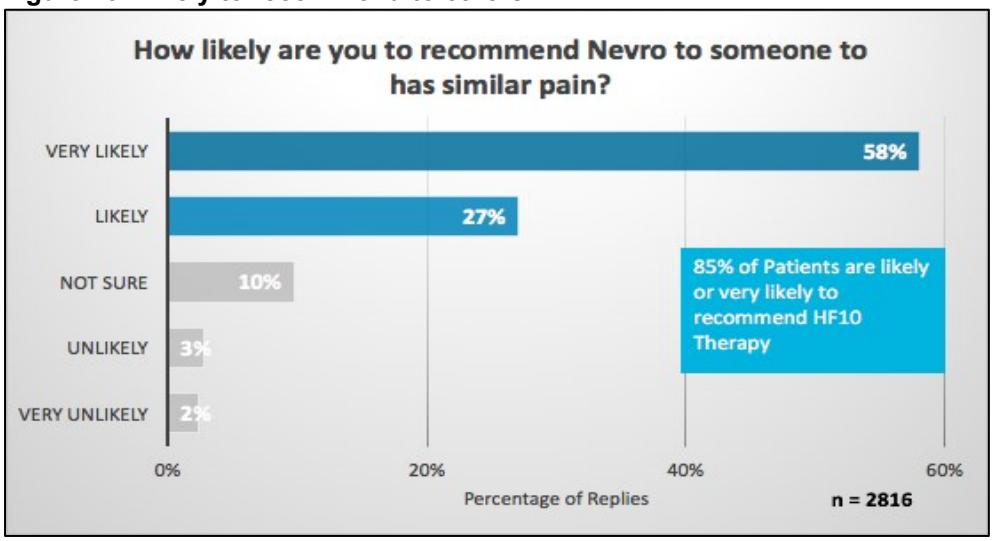
- 87% of patients cited an improvement in HRQoL
- 85% of patients were likely to recommend HF10™ therapy to others
- 88% of patients who previously received traditional low-frequency SCS rated HF10™ therapy as better
- 86% of patients used their remote less than once a week to adjust settings
- 94% of patients charged their device daily or every other day
- 74% of patients were 'satisfied' or 'very satisfied' with the convenience of charging their device
- 99% of patients slept with the device on
- 99% of patients drove with the device on

Figure 18: Change in activity limitations, symptoms, emotions, and overall HRQoL



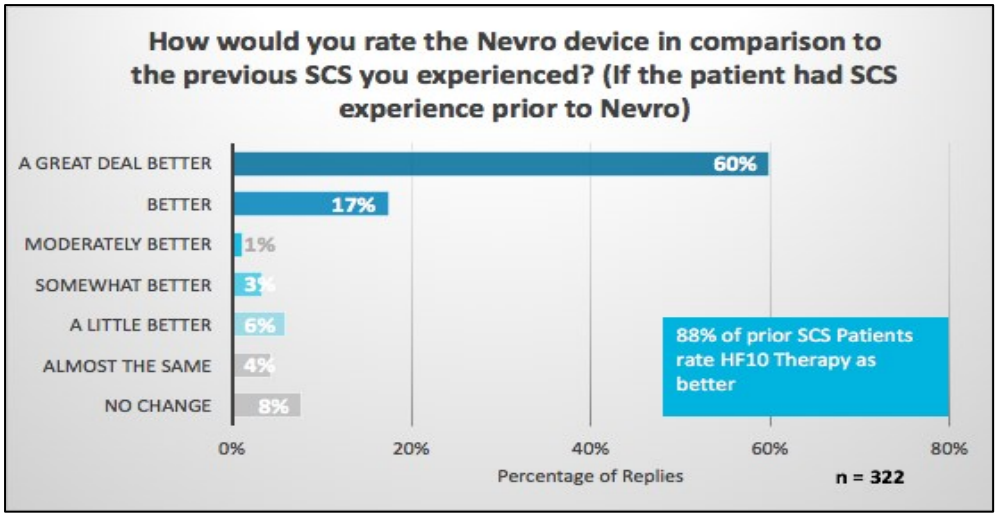
Nevro Corporation. Data on file (31).

Figure 19: Likely to recommend to others



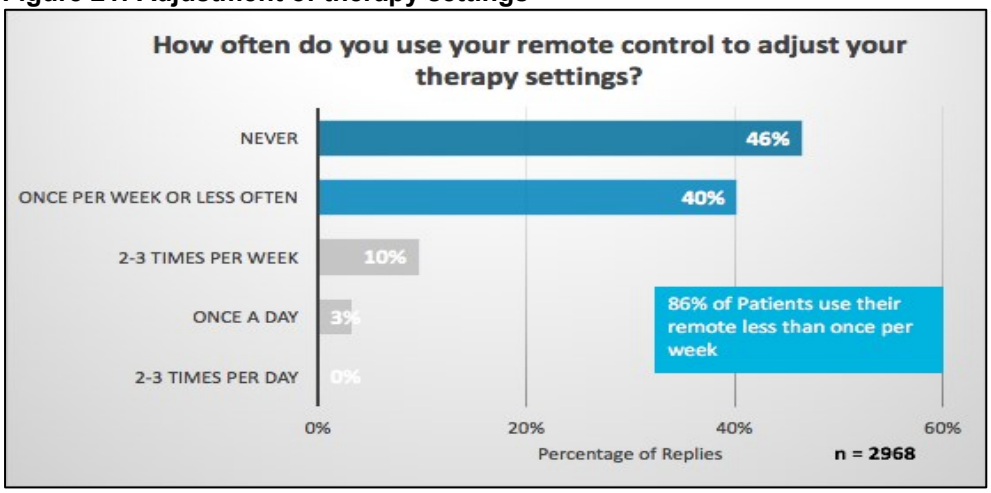
Nevro Corporation. Data on file (31).

Figure 20: Rating of HF10™ therapy in comparison to previous SCS



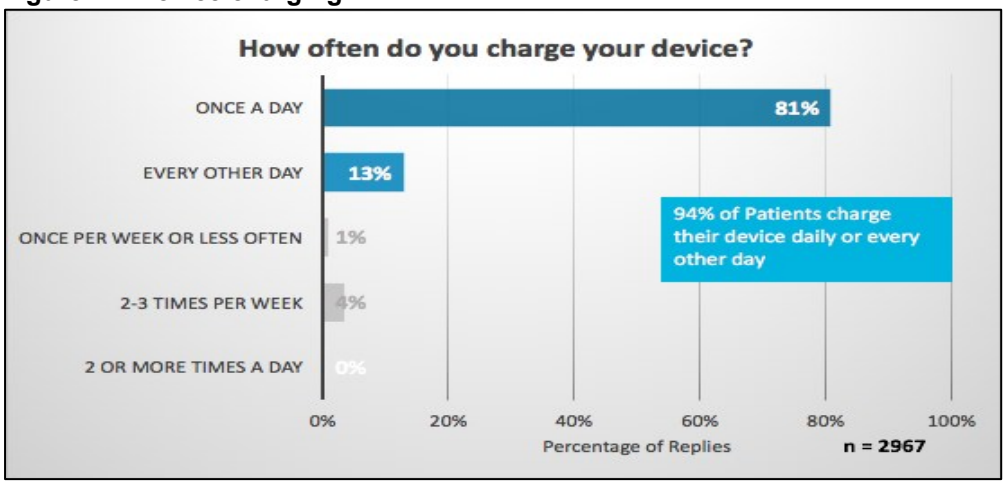
Nevro Corporation. Data on file (31).

Figure 21: Adjustment of therapy settings



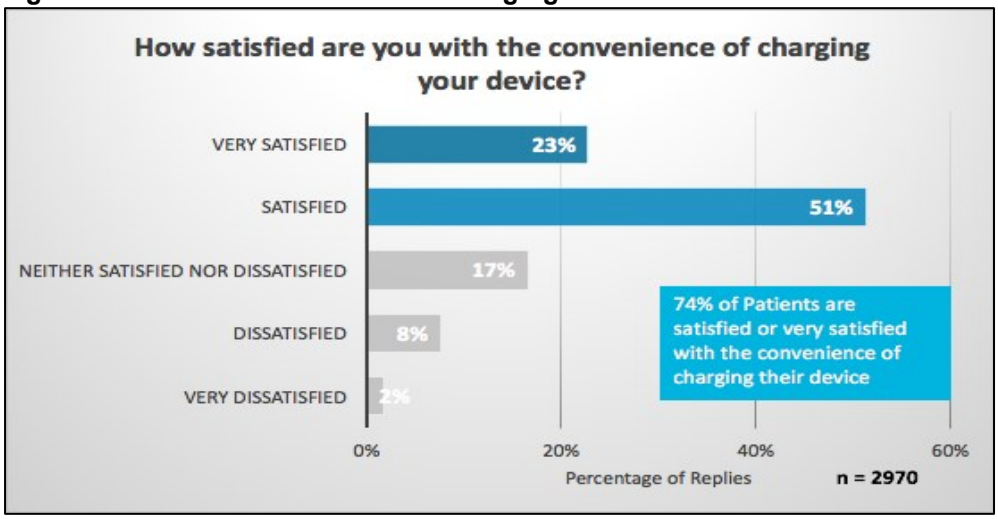
Nevro Corporation. Data on file (31).

Figure 22: Device charging



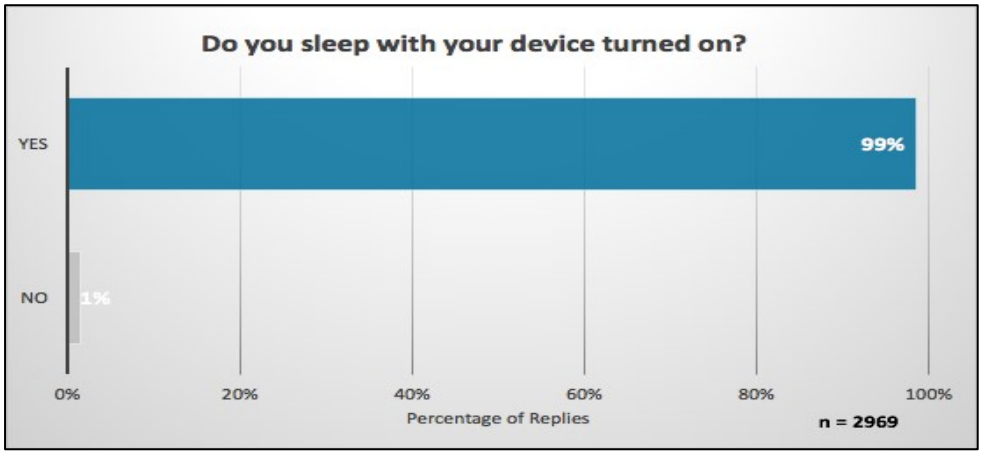
Nevro Corporation. Data on file (31).

Figure 23: Satisfaction with device charging



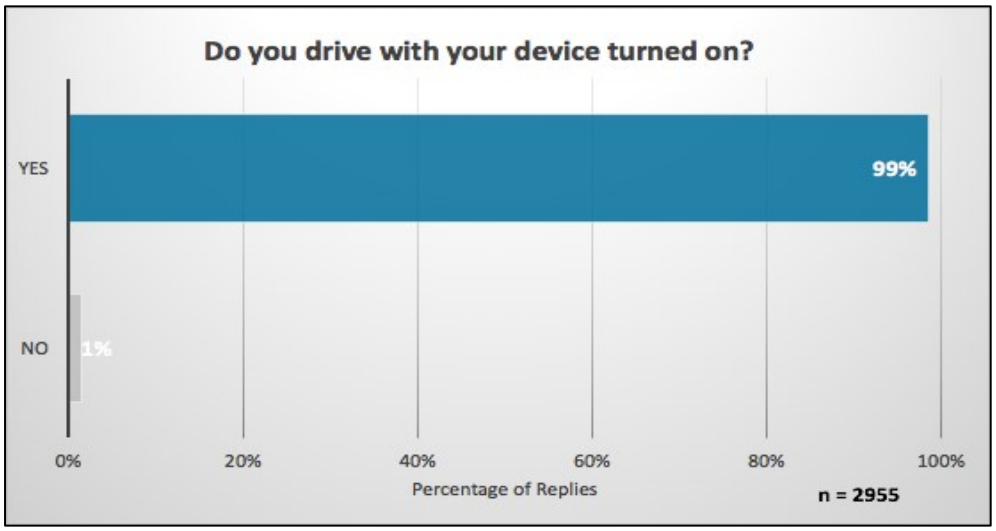
Nevro Corporation. Data on file (31).

Figure 24: Sleeping with device on



Nevro Corporation. Data on file (31).

Figure 25: Driving with device on



Nevro Corporation. Data on file (31).

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The identification of clinical evidence (including adverse events) is described in section 7.1. All studies relevant to this submission are listed in section 7.3. None of these studies were designed primarily to assess the safety of HF10™ therapy. The reporting of AEs varied across the studies.

7.7.2 Provide details of all important adverse events reported for each study.

Table 38: Summary of study-related SAEs at 24 months, SENZA-RCT: Kapural et al. 2016

Study-related SAEs, number of patients (%)	Month 24		
	HF10™ therapy n=101	Traditional low-frequency SCS n=97	Difference (95% CI)
Total	**5.0 (5.0)**	**7.0 (7.2)**	**-2.3 (-10.0 to 5.0), p=0.56**
Wound complications	4.0 (4.0)	3.0 (3.1)	0.9 (-5.5 to 7.2) >.99
Arrhythmia	0.0 (0.0)	1.0 (1.0)	-1.0 (-5.7 to 2.7), p=0.49
Cardiac arrest	0.0 (0.0)	1.0 (1.0)	-1.0 (-5.7 to 2.7), p=0.49
Extradural abscess	0.0 (0.0)	1.0 (1.0)	-1.0 (-5.7 to 2.7), p=0.49
Intracranial hypotension	0.0 (0.0)	1.0 (1.0)	-1.0 (-5.7 to 2.7), p=0.49
Paresis	1.0 (1.0)	0.0 (0.0)	1.0 (-2.9 to 5.5), p<0.99
Post-lumbar puncture syndrome	0.0 (0.0)	1.0 (1.0)	-1.0 (-5.7 to 2.7), p=0.49

Abbreviations: CI, confidence interval; SAEs, serious adverse events; SCS, spinal cord stimulation.
Source: Kapural et al. (2016) (20).

Table 39: Summary of device-related SAEs at 24 months, SENZA-EU: Al-Kaisy et al. (2014)

Device-related SAEs, number of patients (%)	HF10™ therapy
Pocket pain	7.0 (8.4)
Wound infection†	5.0 (6.0)
Lead migration	4.0 (4.8)
Loss of therapy effect	2.0 (2.4)
Sub-optimal lead placement‡	1.0 (1.2)
Skin erosion	1.0 (1.2)

Abbreviations: SAEs, serious adverse events.
† Four infections occurred in the trial phase and one in the permanent phase.
‡ Occurred in the trial phase.
Source: Al-Kaisy et al. (2014) (23).

Table 40: Summary of device-related or possibly device-related AEs†: Tiede et al. (2013)

Device-related or possibly device-related AES, number of patients (%)	HF10™ therapy
Undesirable sensation‡	2.0 (8.0)
Muscle cramps/spasms‡	1.0 (4.0)

Abbreviations: AEs, adverse events; SAEs, serious adverse events.
† There were no SAEs.
‡ Resolved with programming or without any intervention.
Source: Tiede et al. (2013) (29).

In the study by Al-Kaisy et al. (2016) no SAEs occurred. Two patients reported pain/tenderness over the neurostimulator site, one of which required surgical revision; three patients experienced lead migration requiring reprogramming, none required surgical revision.

The following studies did not report AEs:

- Russo et al. (2016) (28)
- Rapcan et al. (2015) (24)
- De Carolis et al. (2017) (26)
-

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

A search of the Medicine and Healthcare Products Regulatory Agency (MHRA) website (13th January 2017) revealed no manufacturer field safety notices or medical device alerts have been issued for HF10™ therapy. A search of the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) website (13th January 2017), identified 15 reports from 12th January 2016 to 31st December 2016. The majority of these events were infection-related, all cases of infection were treated with intravenous antibiotics and no further complications were reported.

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope

The incidence of study-related/device-related SAEs was low across the studies.

In the SENZA-RCT rates of SAEs were higher in the traditional low-frequency SCS group versus the HF10™ therapy group, although the difference was not statistically significant (p=0.56) (20).

Lead migration has been the most frequently reported complication with traditional low-frequency SCS systems with rates ranging from 2.1% to 23% (19). In the SENZA-RCT and the SENZA-EU studies lead migration rates with HF10™ therapy were low in comparison (3.0% and 4.8%), respectively (19, 23).

Patients receiving HF10™ therapy did not report feeling any paresthesias, and therefore did not report any uncomfortable simulation. Whilst 11.3% of patients receiving traditional low-frequency SCS reported the paresthesias as being “uncomfortable” at 24 months (20).

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the ‘Medical Technologies Evaluation Programme Methods Guide’, available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

N/A.

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

A meta-analysis was not considered appropriate due to the degree of heterogeneity between study methodologies. The overall results and critical appraisal for each study are provided in section 7.5 and section 7.6 and a summary of principal findings from all studies is reported in section 7.9.1 below.

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

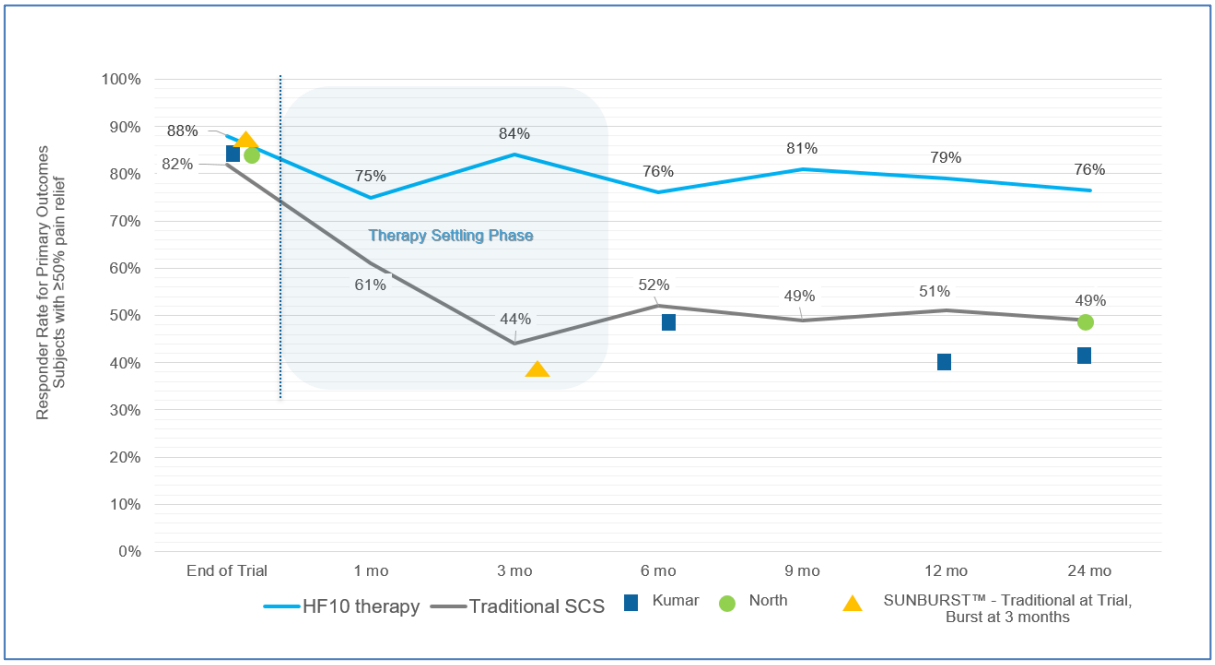
The clinical data presented in section 7.6 demonstrated the benefits of HF10™ therapy. A statement of principal findings from the studies is provided below.

Statistically and clinically significant response rates for back and leg pain with HF10™ therapy

- In the SENZA-RCT, a higher proportion of patients were responders for back pain (≥50% reduction in VAS score) with HF10™ therapy than traditional low-frequency SCS; 84.5% versus 43.8% ($p<0.001$ for superiority) at 3 months (primary endpoint) and 76.5% versus 49.3% at 24 months ($p<0.001$ for superiority), respectively (19, 20)
- A higher proportion of patients were also responders for leg pain in the SENZA-RCT with HF10™ therapy than traditional low-frequency SCS; 72.9% versus 49.3% at 24 months ($p=0.003$ for superiority) (20)
- In the SENZA-EU study, at 24 months 60% of patients were responders (≥50% reduction in VAS score) for back pain ($p<0.001$ compared with baseline) and 71% of patients were responders for leg pain ($p<0.001$ compared with baseline) (23)
- In the study by Tiede at al. (2013), 83% of patients with back and/or leg pain were responders to HF10™ therapy versus 55% of patients with traditional low-frequency SCS ($p<0.001$) (29)
- At 12 months in the study by Rapcan et al. (2015), 67% of patients were responders for back and leg pain ($p<0.001$) (i.e. they still met their pre-implant pain reduction criterion; ≥50% reduction in VAS score) (24)
- In the study by Al-Kaisy et al. (2016), 90% of patients were responders for back pain (>50% reduction in VAS score) at 12 months ($p<0.0001$) (25)

To put the responder results from the SENZA-RCT into context (Figure 26), 24-month data for traditional low-frequency SCS are available from two published RCTs (Kumar et al. (2007), also known as the PROCESS study (5) and the North et al. (2005) study (6)). These two studies were used as the primary evidence base for NICE TAG159 and have been used as a proxy for long-term therapeutic success with traditional low-frequency SCS.

Figure 26: Responder rates: HF10™ therapy versus traditional low-frequency SCS across four RCTs



Abbreviations: RCTs, randomised controlled trials; SCS, spinal cord stimulation.
Source: Kapural et al. (2016) (20), Kumar et al. (2007) (5), North et al. (2005) (6) and the Prodigy™ Neurostimulation System Programming and Reference Clinician Manual (32).

Three month data are also available from an unpublished RCT (SUNBURST™) of St. Jude's Prodigy™ Implantable Pulse Generator (traditional low-frequency SCS) (Figure 26) (32). As shown in Figure 26, the PROCESS, North et al. and SUNBURST™ RCTs show remarkable consistency with similar proportions of patients achieving a ≥50% reduction in pain with traditional low-frequency SCS. However, the responder rates rapidly diminish over time.

In contrast, after the end of the temporary trial phase, HF10™ therapy has a much higher responder rate than traditional low-frequency SCS and this is maintained over the long-term. This therapeutic durability is important to patients, physicians, and payers.

Profound long-term response for back and leg pain with HF10™ therapy

- In the SENZA-RCT, a higher proportion of patients were remitters for back pain (≤2.5 cm VAS score)[f] with HF10™ therapy than traditional low-frequency SCS; 65.9% versus 31.0% (p=0.003 for superiority) at 24 months (20)
- A higher proportion of patients were also remitters for leg pain in the SENZA-RCT with HF10™ therapy than traditional low-frequency SCS; 65.9% versus 39.4% (p<0.001 for superiority) at 24 months (20)

Statistically significant reductions in back and leg pain with HF10™ therapy

- In the SENZA-RCT, back pain (mean VAS score) decreased to a greater degree with HF10™ therapy than traditional low-frequency SCS; relative change 66.9% versus 41.1% (p<0.001 for superiority) at 24 months (20)
- Leg pain also decreased to a greater degree with HF10™ therapy in the SENZA-RCT than traditional low-frequency SCS; relative change 65.1% versus 46.0% (p=0.002 for superiority) at 24 months (20)
- In the SENZA-EU study patients achieved a significant reduction from baseline in back and leg pain with HF10™ therapy at 24 months: back pain; baseline VAS score 8.4 cm versus month 24 VAS score 3.3 cm (p<0.001), leg pain; baseline VAS score 5.4 cm versus month 24 VAS score 2.3 cm (p<0.001) (23)
- Russo et al. (2016) reported a statistically significant reduction in pain (measured by the NPRS scores) with HF10™ therapy in patients with both back and leg pain (p<0.001) and patients with back pain only (p<0.001) at 6 months (28)
- Patients in the study by Tiede et al. (2013) had a 77% reduction (p<0.001) in the overall VAS score from baseline with HF10™ therapy versus a 55% reduction (p<0.001) with traditional low-frequency SCS. A 77% reduction (p<0.001) in the back VAS score from baseline was also achieved with HF10™ therapy (24)

[f] A VAS score of ≤2.5 cm indicates minimal daily impairment or attention to pain.

- In the study by Rapcan et al. (2015), there was a statistically significant reduction ($p<0.001$) in VAS score at 12 months (baseline; 8.7 cm, 12 months; 4.0 cm), with HF10™ therapy (24)
- In the study by Al-Kaisy et al. (2016), there was a significant reduction from baseline in back and leg VAS score at 12 months with HF10™ therapy ($p<0.0001$, $p<0.05$), respectively (25)
- At the time of testing an average pain relief of 70% was achieved with HF10™ therapy in the study by De Carolis et al. (2017) (26)

HF10™ therapy significantly improves functional capacity in patients with back and leg pain

- In the SENZA-RCT, HF10™ therapy patients achieved a favourable distribution of ODI categorisations (i.e. a higher proportion of patients were in the 'minimal disability' and 'moderate disability' categories and a lower proportion of patients were in the 'severe disability' and 'crippled' categories) versus traditional low-frequency SCS ($p=0.02$). At 24 months, 23.5% of patients receiving HF10™ therapy had minimal disability versus 9.9% of patients receiving traditional low-frequency SCS (20)
    - Patient and clinician global impression of change categorisations were also favourable with HF10™ therapy versus traditional low-frequency SCS ($p=0.004$ and $p=0.002$), at 24 months respectively (20)
- There was a significant decrease from baseline in ODI score at 24 months ($p<0.001$) with HF10™ therapy in the SENZA-EU study. At baseline 90% of patients were classified as crippled or severely disabled, and this reduced to 49% at 24 months (23)
    - There was also a significant reduction from baseline in sleep disturbances at 6 months ($p<0.001$) with HF10™ therapy (23)
- In the study by Russo et al. (2016), an 8.6-point reduction in ODI score (21%) was observed at 6 months versus baseline ($p<0.001$) with HF10™ therapy. Improved sitting, standing, and walking tolerances were also reported (28)
- At 12 months ODI scores were significantly lower ($p<0.0001$) compared to baseline with HF10™ therapy (average reduction 47.6%) in the study by Al-Kaisy et al. (2016). At 12 months 45% of patients were in the "minimal disability" category, a 20% improvement compared with baseline, when only 25% were classified as minimally disabled (25)
    - There was also a 54% reduction and 24% improvement from baseline in sleep disturbances and sleep duration at 12 months with HF10™ therapy, respectively (25)

Statistically significant improvements in HRQoL with HF10™ therapy

- In the study by Al-Kaisy et al. (2016) data from SF-36 and EQ-5D questionnaires showed statistically significant improvements from baseline in HRQoL at 12

months with HF10™ therapy (SF-36 physical component score; p<0.0005; SF-36 mental component score; p<0.05 and EQ-5D TTO score; p<0.0001) (25)

- In a survey among 2,977 patients, 87% of patients cited an improvement in HRQoL with HF10™ therapy (31)

Reduction in opioid use with HF10™ therapy

- In clinical studies, many patients reduced or ceased concomitant opioid use (23-25)
    - There was a significant reduction in opioid use in the SENZA-EU study: 86% of patients were taking some form of opioid at baseline, and this reduced to 57% at 24 months (p<0.001) with HF10™ therapy. The mean dose of oral morphine decreased from 84 mg/day at baseline to 27 mg/day at 24 months (p<0.001) (23)
    - In the study by Rapcan et al. (2015), at 12 months 65% of patients had reduced their opioid use by half with HF10™ therapy (24)
    - At 12 months, there was a 64% (72 mg/day) reduction in opioid use with HF10™ therapy compared with baseline, and three patients completely ceased their use of opioids (p=0.0833) in the study by Al-Kaisy et al. (2016) (25)
- Additional evidence from an Australian study also supports a reduction or cessation in opioid use with HF10™ therapy. Opioid use reduced significantly at 6 and 12 months' post implantation compared to baseline with 60-67% of patients ceasing opioid medication (33).

Patient satisfaction with HF10™ therapy is high

- In the SENZA-RCT a higher percentage of patients were very satisfied (60%) with HF10™ therapy versus traditional low-frequency SCS at 24 months (40.4%) (20)
- At 24 months in the SENZA-EU study 85% of patients were satisfied or very satisfied with HF10™ therapy and 88% of patients would recommend HF10™ therapy to others (23)
- In the study by Al-Kaisy et al. (2016) 90% of patients were satisfied or very satisfied with HF10™ therapy and 100% of patients would recommend HF10™ therapy to others (25)
- In a survey among 2,977 patients implanted with HF10™ therapy (31):
    - 87% of patients cited an improvement in HRQoL
    - 85% of patients were likely to recommend HF10™ therapy to others
    - 88% of patients who previously received traditional low-frequency SCS rated HF10™ therapy as better
    - 86% of patients used their remote less than once a week to adjust the setting
    - 94% of patients charged their device daily or every other day

- 74% of patients were ‘satisfied’ or ‘very satisfied’ with the convenience of charging their device
- 99% of patients slept with the device on
- 99% of patients drove with the device on

HF10™ therapy has a similar safety profile to traditional low-frequency SCS, with a low incidence of SAEs

- In the SENZA-RCT, HF10™ therapy and traditional low-frequency SCS had similar rates of SAEs
  - However, patients receiving HF10™ therapy did not report feeling any paraesthesias, and therefore did not report any uncomfortable simulation. In contrast, 11.3% of patients receiving traditional low-frequency SCS reported the paraesthesias as being “uncomfortable”
- The incidence of study-related/device-related SAEs was low with HF10™ therapy across all the studies that reported on safety

Summary

The clinical evidence presented in this submission demonstrates that HF10™ therapy has significantly superior efficacy to traditional low-frequency SCS for the treatment of chronic back and/or leg pain. HF10™ therapy has significantly better rates of response and degree of response which is maintained over the long-term. Functional capacity and HRQoL scores are significantly improved and there are substantial reductions in the need for opioid analgesia with HF10™ therapy. Whilst HF10™ therapy has a similar safety profile to traditional low-frequency SCS, it does not produce the side effect of paraesthesia which is associated with traditional low-frequency SCS systems. It is therefore proposed that HF10™ therapy replaces traditional low-frequency SCS systems in clinical practice.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The evidence base for HF10™ therapy includes a fully powered and rigorously designed RCT (SENZA-RCT).

The SENZA-RCT is the:

- Largest RCT of SCS for back and leg pain to date (n=241 enrolled)
- First RCT to demonstrate direct evidence of superior comparative efficacy and similar safety data for HF10™ therapy versus traditional low-frequency SCS
- First RCT to provide long-term outcomes for patients with both leg and back pain.

In addition, the SENZA-RCT provides data for a high percentage of patients through 24 months (94.4% implanted HF10™ therapy, 87.7% implanted traditional low-frequency SCS).

The outcomes with HF10™ therapy were consistent across studies (section 7.6). The evidence base within this submission demonstrates that HF10™ therapy is a clinically effective treatment. Over the long-term HF10™ therapy demonstrates a superior treatment

option to traditional low-frequency SCS systems (i.e. provides better outcomes for patients) with a similar safety profile. Based on study results, HF10™ therapy is likely to substantially impact the management of patients with chronic leg and back pain.

In the SENZA-RCT study investigators and patients were not masked to the assigned treatment. Masking/blinding of patients and investigators was impractical as:

- Traditional low-frequency SCS produces paraesthesia and HF10™ therapy is paraesthesia-free
- There are also differences in lead placement, intraoperative testing, and device programming between the groups.

Therefore, there is a risk of assessment bias and patient placebo effects. However, given that outcomes were patient reported and the benefits of HF10™ therapy are maintained over 24 months, the likelihood of placebo effects and assessment bias explaining the additional benefits of HF10™ therapy compared to traditional low-frequency SCS is low. Additionally, although specific inclusion and exclusion criteria were applied in the SENZA-RCT, there was heterogeneity in pain diagnoses. However, the majority of patients had FBSS, and the overall heterogeneity in diagnoses reflects clinical practice.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The evidence for HF10™ therapy provided in this submission is directly relevant to the scope. The SENZA-RCT provides a head-to-head comparison of HF10™ therapy and that of the comparator (traditional low-frequency SCS).

Patient benefits

Significant pain relief

The clinical evidence presented in this submission demonstrates that HF10™ therapy provides clinical meaningful and significantly superior pain relief compared to traditional low-frequency SCS for the treatment of chronic back and/or leg pain. In addition, HF10™ therapy significantly improves HRQoL and functional outcomes.

Both leg and back pain relief

HF10™ therapy is superior to traditional low-frequency SCS over the long-term in treating patients with both leg and back pain. Previous RCTs of traditional low-frequency SCS have demonstrated effective pain relief in patients with predominant leg pain only (5, 6).

Paraesthesia-free

With traditional low-frequency SCS systems, paraesthesia can be unpleasant for patients. HF10™ therapy is paraesthesia-free and therefore removes this unwanted side-effect. In addition, effective stimulation can be continued during sleep and when driving or operating machinery, unlike traditional low-frequency SCS systems.

Reduction or cessation in opioid use

In clinical studies, many patients reduced or ceased concomitant opioid use (23-25). Previous large traditional low-frequency SCS system studies did not demonstrate a statistically significant reduction in opioid use (5, 6).

Radiation exposure

With HF10™ therapy, the use of pulsed fluoroscopy instead of continuous fluoroscopy reduces patient and clinician radiation exposure.

System benefits

Paraesthesia-free

As HF10™ therapy is paraesthesia-free, surgical procedure time is more predictable than traditional low-frequency SCS.

Reduction in opioid use

In clinical studies, many patients reduced or ceased concomitant opioid use (23-25). It is expected that this reduction or cessation of opioid use will translate into clinical practice. However, the impact of a reduction or cessation in concomitant opioid use on the healthcare system has not been assessed and therefore this outcome has been excluded from the economic analysis.

Long-term outcomes

The superior long term outcomes of HF10™ therapy compared to traditional low-frequency SCS could potentially reduce follow-up attendance at pain clinics.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

No factors have been identified that may influence the external validity of the study results. The patient population in the studies is reflective of the population in which HF10™ therapy will be used. The benefits of HF10™ therapy reported in the clinical studies are likely to be the same for patients in routine clinical practice.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

N/A.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt.

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt.

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

A systematic literature review was conducted to identify relevant published health economic studies on the use of HF10™ therapy to treat chronic pain of the leg and/or back.

Searches were conducted using the following databases: Medline (PubMed), Medline In-Process (Ovid), Embase (Elsevier), EconLIT (ProQuest), and NHS EED (University of York Centre for Reviews and Dissemination). The searches were limited to publications from 2006 to present, reflecting the timeframe of the existence of the sponsor as a company (Nevro Corp., Redwood City, CA, USA). Search terms combined "spinal cord stimulation" with descriptors specific to HF10™ therapy. The full search strategy is outlined in section 10.3.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Inclusion and exclusion selection criteria for published and unpublished studies are shown in Table 41.

Table 41: Selection criteria used for health economic studies

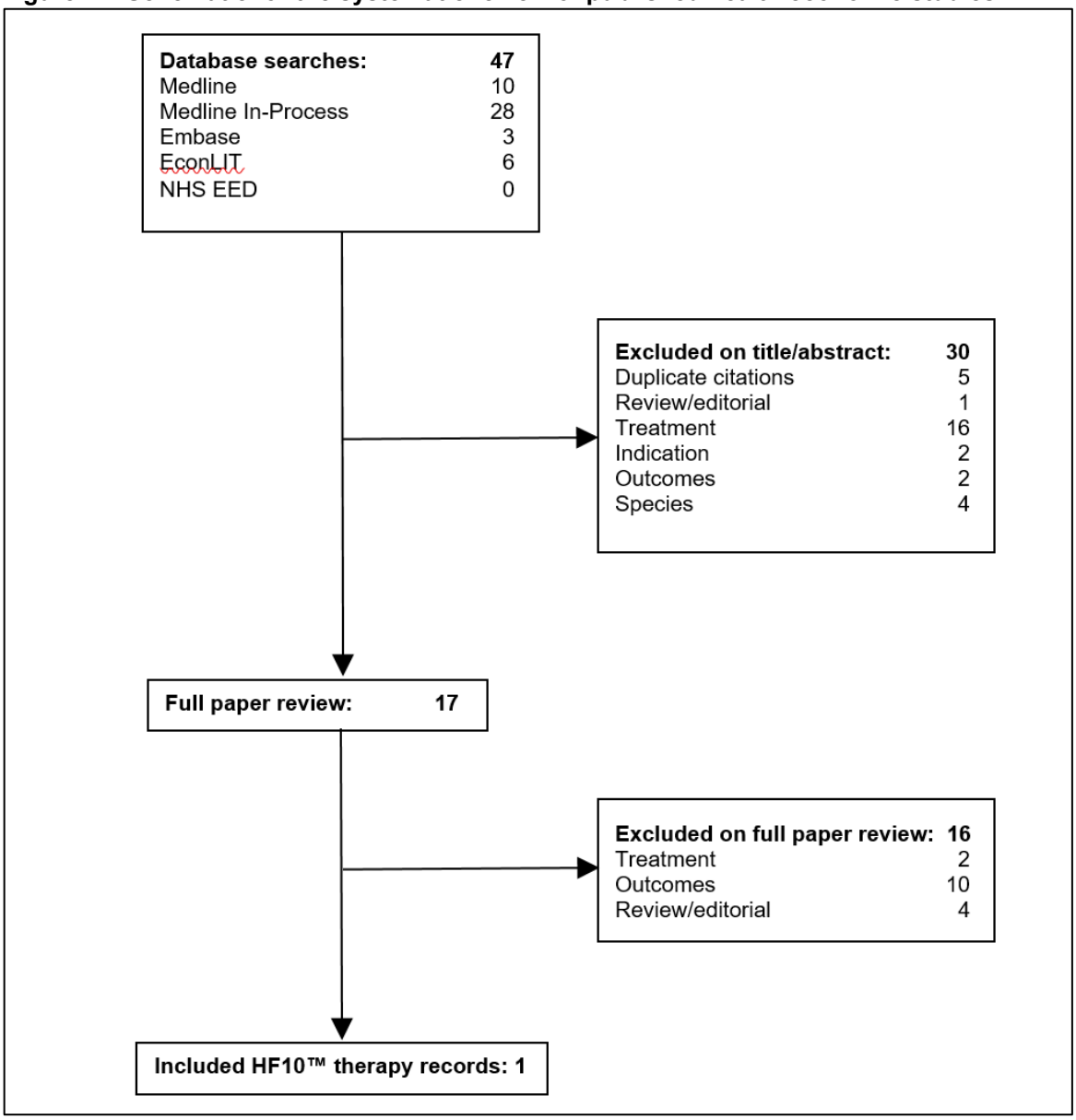
Inclusion criteria	
Population	Patients with chronic neuropathic pain in the legs and/or back
Interventions	HF10™ therapy
Outcomes	Costs, incremental costs, QALYs, budget impact, ICERs
Study design	Economic evaluations
Language restrictions	English language only
Search dates	2006-present
Exclusion criteria	
Interventions	Traditional low-frequency SCS
Outcomes	Data unrelated to safety or efficacy
Study design	Editorials, reviews, letters, book chapters, conference abstracts

Abbreviations: ICERs, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years; SCS, spinal cord stimulation.

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The database searches identified 47 published records potentially relevant health economic studies of HF10™ therapy. Following assessment of title and abstract, 30 of the 47 records were excluded. Following assessment of 17 full-text records, 16 were excluded (Figure 27). One record is included in the final dataset and reports a cost-effectiveness evaluation of HF10™ therapy compared with CMM, reoperation, and traditional low-frequency SCS in patients with FBSS.

Figure 27: Schematic for the systematic review of published health economic studies



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in Table 42

Table 42 shows a summary of the identified evaluation involving costs.

Table 42: Summary list of evaluations involving costs

Study, Year	Location of study	Summary of model	Intervention/ comparator	Patient population	Costs†	Patient outcomes (QALYs)†	Results† (ICER)
Annemans et al. (2014) (34)	Belgium and UK (conducted from perspective of UK NHS)	Cost utility model. First 6 months (decision tree) and subsequent cycles of 3 months (Markov model) over a period of 15 years	HF10™ therapy compared to CMM, reoperation, traditional non-rechargeable low-frequency SCS, and traditional rechargeable low-frequency SCS	Patients with FBSS	**Comparator = CMM** CMM - £80,605,788 TNR-SCS - £92,392,857 TR-SCS - £87,440,887 HF10™ - £86,417,656 **Comparator = reoperation** Reoperation - £82,187,498 TNR-SCS - £92,561,091 TR-SCS - £87,440,887 HF10™ - £86,417,656 **Comparator = TNR-SCS** TNR-SCS - £92,392,857 TR-SCS - £87,440,887 HF10™ - £86,417,656 **Comparator = TR-SCS** [redacted] [redacted] HF10™ - £86,417,656	**Comparator = CMM** CMM - 3,308 TNR-SCS - 4,647 TR-SCS - 4,648 HF10™ - 5,151 **Comparator = reoperation** Reoperation - 3,565 TNR-SCS - 4,439 TR-SCS - 4,648 HF10™ - 5,151 **Comparator = TNR-SCS** TNR-SCS - 4,647 TR-SCS - 4,648 HF10™ - 5,151 **Comparator = TR-SCS** [redacted] [redacted] HF10™ - 5,151	**Comparator = CMM** - TNR-SCS - £8,802 TR-SCS - £5,101 HF10™ - £3,153 **Comparator = reoperation** - TNR-SCS - £11,864 TR-SCS - £4,849 HF10™ - £2,666 **Comparator = TNR-SCS** - TR-SCS - Dominant‡ HF10™ - Dominant **Comparator = TR-SCS** - [redacted] HF10™ - Dominant

Abbreviations: CMM, conventional medical management; FBSS, failed back surgery syndrome; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; QALYs, quality-adjusted life years; SCS, spinal cord stimulation; TNR-SCS, traditional non-rechargeable low-frequency spinal cord stimulation; TR-SCS, traditional rechargeable low-frequency spinal cord stimulation; UK, United Kingdom.

† Simulated cohort of 1,000 patients over 15 years. ‡ Dominant = lower costs and higher QALYs. ¥ Dominated = higher costs and lower QALYs.

≠ [redacted]

8.2.2 Provide a complete quality assessment for each cost-effectiveness study identified. A suggested format is shown in Table 43.

Quality assessment of the health economic study is provided in Table 43.

Table 43: Quality assessment of health economic studies

Annemans et al. (2014) (34)		
Study design	A health economic model of SCS in the UK simulating costs and QALYs over 15 years. A decision tree was used to reflect patient outcomes in the first 6 months and a Markov "state transition" model was used to predict patient outcomes for the remaining 14.5 years.	
Study question	**Response (yes/no/not clear/NA)**	**Comments**
1. Was the research question stated?	Yes	The aim was to evaluate the cost-effectiveness of HF10™ therapy compared to: • CMM • Reoperation • Traditional non-rechargeable low-frequency SCS (TNR-SCS) • Traditional rechargeable low-frequency SCS (TR-SCS)
2. Was the economic importance of the research question stated?	Yes	As new technologies emerge, it is important to evaluate both clinical effectiveness and cost-effectiveness in order to efficiently allocate limited healthcare resources.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes/No	A UK NHS perspective was used. However, the viewpoint was not justified.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	The authors do not explicitly state the rationale for the comparative therapies included. However, it is implied in the introduction section that the comparators reflective current practice in different health care settings.
5. Were the alternatives being compared clearly described?	Yes	The comparative therapies were described along with references to the relevant clinical effectiveness studies.
6. Was the form of economic evaluation stated?	Yes	This is a cost-effectiveness (cost utility) analysis of HF10™ therapy relative to other available treatments for FBSS with calculations of ICERs.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The costs and effects of the available FBSS treatments vary, thus evaluating cost-effectiveness ratios is appropriate.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	The original clinical effectiveness studies were cited.

Annemans et al. (2014) (34)		
Study design	A health economic model of SCS in the UK simulating costs and QALYs over 15 years. A decision tree was used to reflect patient outcomes in the first 6 months and a Markov "state transition" model was used to predict patient outcomes for the remaining 14.5 years.	
Study question	**Response (yes/no/not clear/NA)**	**Comments**
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	The effectiveness estimates were primarily based on SCS RCTs – SENZA, North et al. and Kumar et al. (PROCESS study)
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	No pooling of data was undertaken
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Costs, QALYs, and ICERs were reported.
12. Were the methods used to value health states and other benefits stated?	Yes	In line with NICE recommendations and prior cost-effectiveness analyses for traditional SCS, utility values were assigned to possible outcome states.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Details were reported for the patients included in the HF10™ study while prior publications were referenced for CMM, reoperation, TNR-SCS, and TR-SCS.
14. Were productivity changes (if included) reported separately?	No	Productivity lost through illness or direct cost incurred by patients were not included as a UK NHS perspective was used.
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Sources for cost data input and assumptions used were described.
18. Were currency and price data recorded?	Yes	Prices were reported in British pounds (reference year 2010)
19. Were details of price adjustments for inflation or currency conversion given?	No	There is no discussion of inflation or currency conversion.

Annemans et al. (2014) (34)		
Study design	A health economic model of SCS in the UK simulating costs and QALYs over 15 years. A decision tree was used to reflect patient outcomes in the first 6 months and a Markov "state transition" model was used to predict patient outcomes for the remaining 14.5 years.	
Study question	**Response (yes/no/not clear/NA)**	**Comments**
20. Were details of any model used given?	Yes	The decision tree and Markov model used in the analysis were described in detail.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The model used was based on the previous NICE HTA of TNR-SCS and key parameters were described.
22. Was the time horizon of cost and benefits stated?	Yes	The model simulated outcomes for 1,000 patients over 15 years.
23. Was the discount rate stated?	Yes	A discount rate of 3.5% was applied to future costs and health benefits.
24. Was the choice of rate justified?	Yes	The discount rate applied is consistent with NICE guidelines.
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	Probabilistic analyses were undertaken and costs were presented as means and 95% CIs. The statistical analysis of this economic model included sensitivity analyses.
27. Was the approach to sensitivity analysis described?	Yes	The sensitivity analyses used were described.
28. Was the choice of variables for sensitivity analysis justified?	Yes	Variables included lower follow-up cost, responder rate, device longevity, and device cost.
29. Were the ranges over which the parameters were varied stated?	Yes	The ranges of the variables were described.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	All 3 types of SCS systems were compared to each other as well as to CMM and reoperation.
31. Was an incremental analysis reported?	Yes	Incremental costs and QALYs were calculated and results were presented as ICERs.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs and QALYs were reported in a disaggregated form, ICERs were reported in an aggregated form.

Annemans et al. (2014) (34)		
Study design	A health economic model of SCS in the UK simulating costs and QALYs over 15 years. A decision tree was used to reflect patient outcomes in the first 6 months and a Markov "state transition" model was used to predict patient outcomes for the remaining 14.5 years.	
Study question	**Response (yes/no/not clear/NA)**	**Comments**
33. Was the answer to the study question given?	Yes	HF10™ therapy was found to be more cost-effective over 15 years than CMM, reoperation, TNR-SCS, and TR-SCS.
34. Did conclusions follow from the data reported?	Yes	The conclusions were supported by the data.
35. Were conclusions accompanied by the appropriate caveats?	Yes	The strengths and limitations of the economic analysis were discussed.
36. Were generalisability issues addressed?	No	There is no discussion of the generalisability of the conclusions.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Abbreviations: CMM, conventional medical management; FBSS, failed back surgery syndrome; ICERs, incremental cost-effectiveness ratios; N/A, not applicable; NHS, National Health Service; QALYs, quality-adjusted life years; SCS, spinal cord stimulation; TNR-SCS, traditional non-rechargeable low-frequency spinal cord stimulation; TR-SCS, traditional rechargeable low-frequency spinal cord stimulation; UK, United Kingdom.

In summary, the Annemans et al. study was judged to be of high quality and concluded that HF10™ therapy is cost-effective compared to CMM and reoperation, and domninant compared to TNR-SCS and TR-SCS (31).

9 De novo cost analysis

9.1 Description of de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

NICE TAG159 (published in 2008), recommends the use of spinal cord stimulation (SCS) as a treatment option for selected adults with chronic pain of neuropathic origin. To assess the cost-effectiveness of SCS for NICE TAG159, a two-stage cost- utility model developed by the School of Health and Related Research (ScHARR), an independent economic assessment group, was utilised (35): a decision tree model for the first 6 months after SCS implantation, and a Markov "state transition" over the long-term (15-years) (35). This model structure was originally developed by Taylor and Taylor (2005) to assess the cost-effectiveness of SCS compared to conventional medical management (CMM)[g] for patients with failed back surgery syndrome (FBSS) (36). Based on the results of the ScHARR model, NICE concluded that SCS is cost-effective, compared to CMM or reoperation (NICE TAG159) for the treatment of chronic pain of neuropathic origin. The model developed for NICE TAG159 was subsequently updated by Taylor et al. (2010) to include clinical and cost data from Kumar et al. (2007) (PROCESS study - a randomised controlled trial comparing traditional low-frequency SCS with CMM), which was unavailable during the NICE appraisal (NICE TAG159) (37). Taylor et al. also assessed the cost-effectiveness of traditional low-frequency traditional low-frequency nonrechargeable SCS systems (TNR-SCS) versus rechargeable SCS systems (TR-SCS) (37). The analysis by Taylor et al. (2010) concluded that TNR-SCS is more cost-effective compared with CMM or reoperation, and TR-SCS is more cost-effective than TNR-SCS, provided the implant lifetime (referred to as device longevity from this point onwards in the submission) of TNR-SCS devices is ≤4 years.

The model developed for NICE TAG159 was also reproduced by Annemans et al. (2014) to evaluate the cost-effectiveness of HF10™ therapy (high-frequency SCS system) compared to CMM, reoperation, TNR-SCS and TR-SCS (34). Annemans et al. concluded that HF10™ therapy is cost-effective compared to CMM, reoperation, TNR-SCS and TR-SCS (Table 42) (34).

A detailed review of the Annemans et al. model was undertaken to assess suitability for use in this submission. Whilst high quality, a de-novo model was developed using the same model structure as Annemans et al. for the following reasons:

- To align more closely with the NICE TAG159 model
- To include the most reliable estimates of NHS and Personal Social Service (PSS) costs of HF10™ therapy + CMM relative to TNR-SCS + CMM and TR-SCS + CMM

[g] CMM typically includes pharmacological treatments, non-pharmacological interventions (e.g. physiotherapy, acupuncture, nerve blocks with injected local anaesthetics, transcutaneous electrical nerve stimulation) and psychological therapies (e.g. cognitive behavioural therapy, stress management, counselling).

- To facilitate the inclusion of differential device explant rates in year 1 and year 2

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

Adult patients (≥18 years) experiencing chronic pain despite CMM in line with NICE TAG159 as outlined in the final scope.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

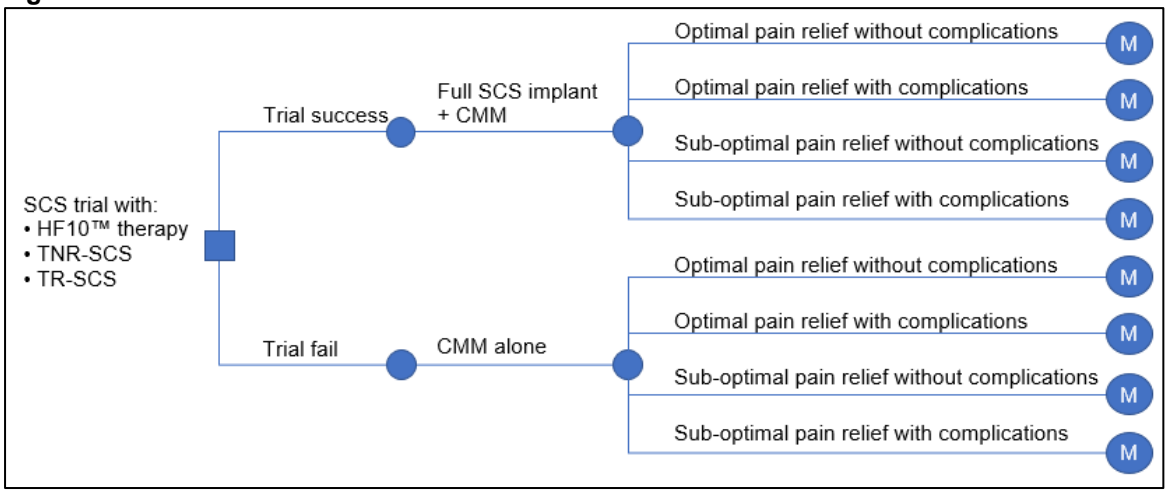
The comparator used in the cost analysis is traditional low-frequency SCS as outlined in the final scope. The analysis includes a comparison of HF10™ therapy + CMM with both TNR-SCS + CMM and TR-SCS + CMM. The model assumes that CMM remains available as an adjunct treatment to HF10™ therapy and TNR-SCS/TR-SCS as per clinical practice.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

A decision tree model is used to explore the clinical pathway of patients in the short-term (first 6 months), (Figure 28). In the decision tree, all patients allocated to SCS undergo a trial phase of SCS to assess acute pain relief, as per clinical practice. Patients who achieve satisfactory pain relief (trial success typically defined as a ≥50% reduction in pain), receive a permanent SCS implant and patients who fail the trial phase receive CMM alone. Post permanent implantation the decision tree model considers the initial 6-month response to treatment with or without complications for HF10™ therapy + CMM versus TNR-SCS + CMM and versus TR-SCS + CMM.

Figure 28: Six-month decision tree



Abbreviations: CMM, conventional medical management; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

After 6 months patients enter a Markov model which is used to explore the clinical pathway of patients over the long-term (15 years). For consistency with the model and assumptions accepted by NICE in TAG159, the base case analysis utilises a 15-year time horizon. It is felt

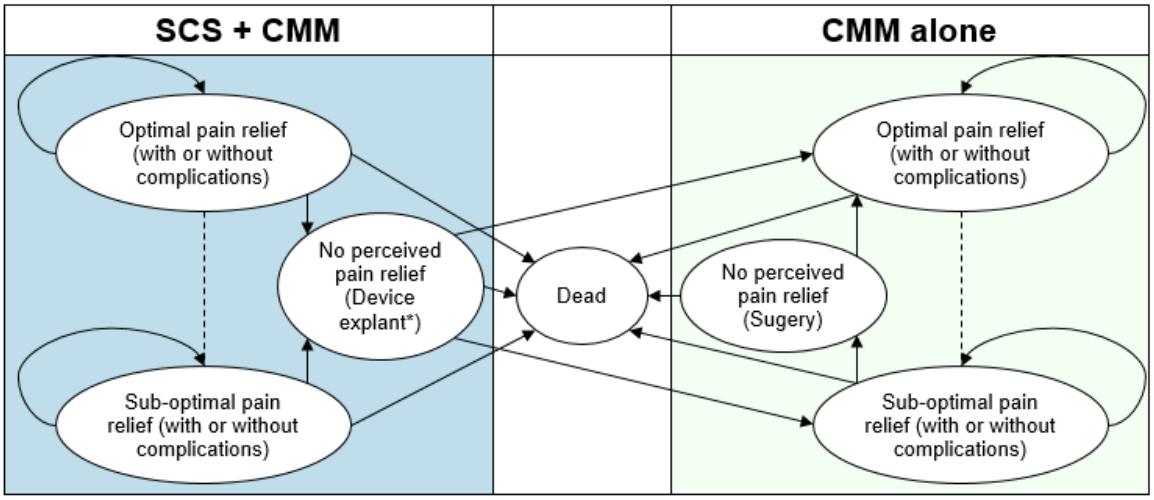
this is appropriate in the base case given the chronic nature of the condition and the longevity of the devices, particularly those utilising a rechargeable battery.

During each 3-month cycle patients in the SCS + CMM arm remain in their current health state (optimal or sub-optimal pain relief), unless they:

1. Have the SCS device removed due to insufficient pain relief, intolerable paraesthesia[h] or other complication (e.g. surgical site infection).
2. Undergo another spinal surgery due to insufficient pain relief in the CMM alone arm.
3. Die.

It should be noted that mortality is included for completeness, there is no mortality implication associated with the SCS devices, and surgery related mortality has also not been considered. Although patients remain in the optimal or sub-optimal pain relief state, those with an SCS device can experience device related complications that do not require a device explant in each cycle.

Figure 29: Schematic of the long-term Markov model



Abbreviations: CMM, conventional medical management; SCS, spinal cord stimulation.
* SCS devices may also be removed due to paraesthesia and other adverse events.

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The model structure reflects that used and accepted by NICE in TAG159 to assess the cost-effectiveness of traditional low-frequency SCS and captures the costs and outcomes expected in clinical practice. The approach taken also reflects Kapural et al. (2015), the SENZA-RCT

[h] Traditional low-frequency SCS systems induce paraesthesia, a 'tingling' or 'buzzing' sensation to mask the patient's pain. An intra-operative step known as 'paraesthesia mapping' is required, during trial stimulation and when permanently implanting traditional low-frequency SCS systems. When the traditional low-frequency SCS system is active, paraesthesia is always present and can be unpleasant: many patients find this a disturbing side effect of traditional low-frequency SCS systems. HF10™ therapy is paraesthesia-free and therefore removes this unwanted side-effect.

comparing HF10™ therapy with traditional low-frequency SCS, and the pathway of care outlined in section A (19).

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Table 44: Assumptions used in the model

Assumption	Justification
Complications occur equally in patients with optimal and sub-optimal pain relief	Same assumption used in NICE TAG159 model. No other publicly available data.
Proportion of patients receiving a back reoperation: 5%	Same assumption used in NICE TAG159 model. No other publicly available data.
Device longevity of TNR-SCS: 4 years	Assumption based the figure used in NICE TAG159 model and Taylor et al. (2010) (37). This was supported by a review of TNR-SCS physician manuals which suggest a range of 2-6 years. This range is wide because the power requirements and duration of daily usage varies substantially between patients.
Device longevity of TR-SCS and HF10™ therapy: 10 years	HF10™ therapy regulatory approval has been granted for a battery life of at least 10 years of continuous use (i.e. it is expected that the patient will not have to receive a new neurostimulator for at least 10 years). Therefore, this is a conservative assumption for HF10™ therapy. A review of TR-SCS physician manuals suggest a range of 5-12 years device longevity. Most manuals reviewed typically reported a device longevity of 9-10 years. However, there was one device system (Precision Montage MRI System IPG, Boston Scientific) that reported a device longevity of at least 5 years.
Patients who have an unsuccessful SCS trial will receive CMM alone and the likelihood of optimal pain relief is 9.3%	Same assumption used in NICE TAG159 model. No other publicly available data.
All CMM costs are comparable with that of Kumar et al. (2007) (PROCESS study) (5) and applied equally in patients with optimal and sub-optimal pain relief	Same assumption used in NICE TAG159 model. No other publicly available data. This is a conservative assumption as HF10™ therapy is likely to reduce opioid use (see section 3.9) and clinic visits (see section 3.10) and these have not been included in the model.
All surgery costs (screening, implantation, explanation etc.) are assumed to be equal for HF10™ therapy and TNR-SCS and TR-SCS	No publicly available data. This is a conservative assumption. HF10™ therapy is paraesthesia-free and unlike traditional TR-SCS/TNR-SCS there is no need to wake patients during implantation to assess paraesthesia (see section 3.9). As a result, surgery time could be shorter with HF10™ therapy. Since this outcome has not been the

	subject of a study and therefore data are not available, a reduction in surgery time with HF10™ therapy has not been included in the model.
Clinical data inputs for TNR-SCS are assumed to be the same as TR-SCS	There are no data showing a differential in clinical outcomes between rechargeable and non-rechargeable devices. Since these devices all deliver low-frequency paraesthesia dependant SCS there is no justification to assume a differential clinical benefit. The main differences between the two are the cost of the devices and device longevity (battery life). Additionally, NICE TAG159 accepted the clinical outcomes of TNR-SCS and TR-SCS would be equivalent.
When patients enter the optimal or sub-optimal pain relief states, they remain in this state unless the SCS system fails or they have a reoperation	This is a conservative assumption. Retrospective long-term data demonstrates that pain relief at 6 months is maintained over 4 years with HF10™ therapy in a cohort of FBSS patients (38). In contrast, there is evidence to suggest that pain relief diminishes over time with traditional low-frequency SCS (5, 6) (see clinical section 7.9).
It is assumed that there is no incremental mortality risk associated with SCS implantation. All-cause mortality is included within the analysis for completeness.	There is no evidence to suggest a mortality risk associated with SCS implantation. Same assumption used in NICE TAG159 model.

Abbreviations: CMM, conventional medical management; FBSS, failed back surgery syndrome; SCS, spinal cord stimulation; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

9.1.7 Define what the model's health states are intended to capture.

In the Markov model patients can be in one of six mutually exclusive health states as follows over the time horizon:

1. Optimal pain relief (defined as ≥50% reduction in VAS score for leg pain) with no complications (complications are generally related to technical complications of the device (e.g. lead migration) or other complications (e.g. infections).
2. Optimal pain relief with complications.
3. Sub-optimal pain relief (some pain relief but <50% reduction in VAS score for leg pain) with no complications.
4. Sub-optimal pain relief with complications.
5. No perceived pain relief (no impact on the pain experienced by the patient despite a well-functioning device). Consequently, this relates to a change in treatment strategy (e.g. device explant/removal or subsequent reoperation) and reverting to CMM alone. Patients may also have a device explant due to intolerable paraesthesia or other complications (e.g. surgical site infection)
6. Death (all-cause mortality).

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Key additional features of the model are presented in Table 45.

Table 45: Key features of the model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	15 years	As per NICE TAG159 model and reflective of previous observational data Kumar et al. (PROCESS study) (5)	Simpson et al. (2009) (35)
Discount of 3.5% for costs	3.5%	All costs beyond one year are discounted at a rate of 3.5% as per the NICE reference case	NICE Guide to the Methods of Technology Appraisal (2013) (40)
Perspective (NHS/PSS)	NHS/PSS	The model reports costs from an NHS/PSS perspective as per the NICE reference case	NICE Guide to the Methods of Technology Appraisal (2013) (40)
Cycle length	3 months	As per NICE TAG159 model and other SCS economic analyses	Simpson et al. (2009) (35)

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; SCS, spinal cord stimulation.

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

The clinical data used in the decision tree (first 6 months) for trial success and optimal pain relief (a ≥50% reduction in leg pain from baseline) in the base case are taken from the SENZA-RCT (19). A scenario analysis has also been conducted using a ≥50% reduction in back pain from baseline (section 9.5.7). Non-serious complications were adverse events not resulting in a device explant including events such as lead migration, device dislocation, implant site pain, surgical site infection, delayed wound healing and paraesthesia and were derived from patient level analysis of the SENZA-RCT. Probabilities for optimal pain relief without complications, optimal pain relief with complications, sub-optimal pain relief without complications and sub-optimal pain relief with complications are calculated from the SENZA-RCT. The base case values are outlined in Table 46.

Table 46: Clinical data variables in the decision tree (6-months) [CONTAINS AiC]

Model parameter	Base case value (95% CI)	Source
Trial success		
HF10™ therapy	92.8% (87.6% to 97.9%)	Kapural et al. (2015) (19)
TR-SCS/TNR-SCS	88.0% (81.4% to 94.7%)	Kapural et al. (2015) (19)
Optimal pain relief (leg pain, 6 months)		

HF10™ therapy	80.9% (72.7% to 89.1%)	Kapural et al. (2015) (19)
TR-SCS/TNR-SCS	54.4% (43.5% to 65.2%)	Kapural et al. (2015) (19)
CMM alone	9.3% (8.4% to 10.2%)	Taylor et al. (2010) (37)
Non-serious complications (6 months)		
HF10™ therapy	[redacted]	SENZA-RCT, data on file (31)
TR-SCS/TNR-SCS	[redacted]	SENZA-RCT, data on file (31)
Calculated values from the SENZA-RCT		
Optimal pain relief without complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT
TR-SCS/TNR-SCS	[redacted]	Calculated from SENZA-RCT
Optimal pain relief with complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT
TR-SCS/TNR-SCS	[redacted]	Calculated from SENZA-RCT
Sub-optimal pain relief without complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT
TR-SCS/TNR-SCS	[redacted]	Calculated from SENZA-RCT
Sub-optimal pain relief with complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT
TR-SCS/TNR-SCS	[redacted]	Calculated from SENZA-RCT

Abbreviations: CI, confidence interval; CMM, conventional medical management; RCT, randomised controlled trial; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

In the Markov model long-term complication (non-serious) rates and device explant rates are based on patient level data from the SENZA-RCT not reported in Kapural et al. (2015) (19) or Kapural et al. (2016) (20), (Table 47).

The SENZA-RCT recorded the number of patients experiencing non-serious complicatons during the study period. However, some patients experienced multiple complications. As a result, an analysis of patient level data was performed to determine the number of complications. The analysis focused on non-serious complications[i], that did not result in a device explant.

Some complications require device explant to achieve resolution. Whilst not reported in Kapural et al. (2015) (19) or Kapural et al. (2016) (20), within the SENZA-RCT there were

[i] Complications that did not lead to death, serious deterioration in the health of the subject, fetal distress, fetal death, or a congenital abnormality or birth defect.

three broad classifications of complications that resulted in a device explant; ineffective pain control, intolerable paraesthesia and other adverse events (e.g. surgical site infections, patient falls etc). Device explants were considered separately from the previously mentioned non-serious complications for two time periods; from implantation to month 6 and from month 6 to the end of the two-year study period. The first period reflects the time horizon of the decision tree, the second was annualised for use in the long-term Markov model (Table 47).

To identify the explant rates in Year 1 and Year 2 for HF10™ therapy and for TNR-SCS/TR-SCS devices a patient level data analysis of the SENZA-RCT (31) was conducted. Results are presented in Table 41.

[redacted] In Year 1, there were higher rates of explants for TNR-SCS/TR-SCS compared to HF10™ therapy due to intolerable paraesthesia. In Year 2 the difference between HF10™ therapy and TNR-SCS/TR-SCS was mainly influenced by a lack of therapeutic effect with TNR-SCS/TR-SCS. As no HF10™ therapy data currently exists beyond Year 2 from the SENZA-RCT, the analysis conservatively assumes that the explant rate for HF10™ therapy and TNR-SCS/TR-SCS is equivalent from Year 3 onwards using a rate of 3.2% per annum as previously assumed in the NICE TAG159 model (35) and subsequently in the analysis by Taylor et al. (2010) (37). This assumption is likely to be conservative, as the clear benefit in explant rates between HF10™ therapy and TNR-SCS/TR-SCS is not included from Year 3 onwards. In addition, a very conservative analysis was performed assuming no difference in explant rates between HF10™ therapy and TNR-SCS/TR-SCS in Year 1 and Year 2 using the 3.2% assumed in the NICE TAG159 model (35) and subsequently in Taylor et al. (2010) (37).

Table 47: Clinical data variables in the Markov model (Contains AiC)

Model parameter	Base case value (95% CI)	Source
Non-serious complications (beyond 6 months)		
HF10™ therapy	[redacted]	SENZA-RCT, data on file (31)
TNR-SCS/TR-SCS	[redacted]	SENZA-RCT, data on file (31)
Explant rate (Year 1)		
HF10™ therapy	[redacted]	SENZA-RCT, data on file (31)
TNR-SCS/TR-SCS	[redacted]	SENZA-RCT, data on file (31)
Explant rate (Year 2)		
HF10™ therapy	[redacted]	SENZA-RCT, data on file (31)
TNR-SCS/TR-SCS	[redacted]	SENZA-RCT, data on file (31)
Explant rate (Year 3 and beyond)		
HF10™ therapy	3.2% (0% to 15.8%)	Simpson et al. (2009) (35)
TNR-SCS/TR-SCS	3.2% (0% to 15.8%)	Simpson et al. (2009) (35)

Abbreviations: CI, confidence interval; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

A number of other variables are required for the Markov model. These variables have been used previously in the NICE TAG159 model (35) and subsequently by Taylor et al. (2010) (37) and are reported in Table 48.

Table 48: Other clinical data variables in the Markov model

Model parameter	Base case value (95% CI)	Source
Annual death rate	0.8% (0.7% to 0.9%)	Office National Statistics (England) (41)
Proportion of patients receiving a reoperation per annum	5.0% (4.5% to 5.5%)	Simpson et al. (2009) (35)
Proportion of patients achieving optimal pain relief post surgery after a reoperation	19.0% (17.1% to 20.9%)	Simpson et al. (2009) (35)

Abbreviations: CI, confidence interval.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Patients are assumed to stay in the optimal or sub-optimal pain relief health state for the duration of the model unless one of the following occurs; device explant (due to ineffective pain relief, intolerable paraesthesia, or other complications), a subsequent spinal surgery, or death. The proportion of patients undergoing a subsequent spinal surgery and the success rate of this surgery are based on the assumptions previously used in the NICE TAG159 model (35).

Costs of CMM are assumed to accrue in each model cycle, based on the patient's pain relief status, reflecting previous economic analyses.

One of the key differentiators between TNR-SCS and TR-SCS is device longevity. When the battery in TNR-SCS/TR-SCS has depleted or it is no longer recharging, it needs to be replaced. As there are a number of different TNR-SCS and TR-SCS manufacturers, models and usage settings it is challenging to provide a definitive device longevity. An ad hoc search of TNR-SCS and TR-SCS physician manuals was undertaken.

The device longevity for TNR-SCS ranged from 2-6 years. This range is wide because the power requirements and duration of daily usage varies substantially between patients. In previous economic evaluations, including NICE TAG159 and Taylor et al. (2010) (37), the device longevity for a TNR-SCS was estimated at 4 years, based on the midpoint of the observations of Kumar et al. (2002) which reported an average lifespan of between 3.5 and 4.5 years (42). Therefore, a mean device longevity of 4 years was assumed for TNR-SCS.

For the purpose of this analysis it is assumed that HF10™ therapy and TR-SCS have a device longevity of 10 years and this is varied between 9 and 25 years in sensitivity analysis. The device longevity for TR-SCS ranged from 5-12 years in the physician manuals. However, a previous economic evaluation, Hornberger et al. (2008) (43), suggested that based on engineering testing, a TR-SCS may last for 25 years. For HF10™ therapy, regulatory approval has been granted for a battery life of at least 10 years of continuous use (i.e. it is expected that the patient will not have to receive a new neurostimulator for at least 10 years) and engineering testing by the manufacturer suggests that the device may last for up to 25 years

with typical usage settings. Consequently, the point estimate of 10 years is likely to be conservative.

It is important when considering device longevity to take into account comparative common patterns of use, e.g. some patients may continually use the device 24 hours per day whilst others may continually use the device for only a few hours per day. Paraesthesia is likely to be a factor in usage patterns for traditional low-frequency SCS. Many patients discontinue TR-SCS usage at night to avoid uncomfortable stimulation while sleeping and the use of TNR-SCS are specified at 12 hours per day to increase device longevity.

HF10™ therapy is typically used 24 hours per day.

[redacted] A survey of patients using HF10™ therapy reported that 99% of patients sleep (of 2,969 total respondents) and 99% drive (of 2,955 total respondents) with the stimulation switched on (31).

Table 49: Device longevity

Model parameter	Base case value (Range)	Source
Device longevity (years)		
HF10™ therapy	10 (8 to 25)	HF10™ regulatory approval has been granted for a battery life of at least 10 years of continuous use (i.e. it is expected that the patient will not have to receive a new neurostimulator for at least 10 years)
TR-SCS	10 (8 to 25)	Assumption based on review of physician manuals and previous economic evaluations
TNR-SCS	4 (2 to 6)	Assumption based on review of physician manuals and previous economic evaluations

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

N/A.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Yes, adverse events were included in the cost model detail previously provided in section 9.2.1.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The applicability of available or estimated model parameters and inputs used in the analysis were assessed by the following advisors and were deemed relevant:

[redacted]

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in Table 50.

A summary of all model variables are provided in Table 50.

Table 50: Additional variables applied in the cost analysis

Model parameter	Base case value (95% CI or range)	Source
Trial success		
HF10™ therapy	92.8% (87.6% to 97.9%)	Kapural et al. (2015) (19)
TNR-SCS/TR-SCS	88.0% (81.4% to 94.7%)	Kapural et al. (2015) (19)
Optimal pain relief (leg pain, 6 months)		
HF10™ therapy	80.9% (72.7% to 89.1%)	Kapural et al. (2015) (19)
TNR-SCS/TR-SCS	54.4% (43.5% to 65.2%)	Kapural et al. (2015) (19)
CMM alone	9.3% (8.4% to 10.2%)	Taylor et al 2010 (37)
Non-serious complications (6 months)		
HF10™ therapy	[redacted]	SENZA-RCT, data on file (31)
TNR-SCS/TR-SCS	[redacted]	SENZA-RCT, data on file (31)
Annual death rate†	0.81% (0.7% to 0.9%)	Office National Statistics (England) (41)
Proportion of patients receiving a reoperation	5.0% (4.5% to 5.5%)	Simpson et al. (2009) (35)
Proportion of patients obtaining optimal pain relief post-surgery after a reoperation	19.0% (17.1% to 20.9%)	Simpson et al. (2009) (35)
Explant rate (Year 1)		
HF10™ therapy	[redacted]	SENZA-RCT, data on file
TNR-SCS/TR-SCS	[redacted]	SENZA-RCT, data on file
Explant rate (Year 2)		

HF10™ therapy	[redacted]	SENZA-RCT, data on file
TNR-SCS/TR-SCS	[redacted]	SENZA-RCT, data on file
Explant rate (Year 3)		
HF10™ therapy	3.2% (0% to 15.8%)	Simpson et al. (2009) (35)
TNR-SCS/TR-SCS	3.2% (0% to 15.8%)	Simpson et al. (2009) (35)
Non-serious complications (beyond 6 months)		
HF10™ therapy	[redacted]	SENZA-RCT, data on file (31)
TNR-SCS/TR-SCS	[redacted]	SENZA-RCT, data on file (31)
Device longevity (years)		
HF10™ therapy	10 (8 to 25)	Conservative assumption: HF10™ regulatory approval has been granted for a battery life of at least 10 years of continuous use (i.e. it is expected that the patient will not have to receive a new neurostimulator for at least 10 years).
TR-SCS	10 (8 to 25)	Assumption based on review of physician manuals and previous economic evaluations
TNR-SCS	4 (2 to 6)	Assumption based on review of physician manuals and previous economic evaluations

Abbreviations: CI, Confidence interval; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
† All-cause mortality (England) and assumed to be independent of health state.

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

National Schedule of Reference Costs 2015-16:

- Currency Code AB12Z: Insertion of Neurostimulator for Pain Management - £15,637 (national average unit cost, elective inpatient)

Payment by Results Tariff: Annex A 2017/18 National Prices and National Tariff Workbook:

- HRG Code AB12Z: Insertion of Neurostimulator for Pain Management - £2,509 (Combined day case/ordinary elective spell tariff)

SCS devices are covered by the High Cost Device List (HCDL), i.e. the costs of the devices are reimbursed to centres in addition to the tariff.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

OPCS code:

- A48.3: Implantation of neurostimulator adjacent to the spinal cord
- A48.4 Attention to neurostimulator adjacent to spinal cord
- A48.5 Reprogramming of neurostimulator adjacent to spinal cord
- A48.6 Removal of neurostimulator adjacent to spinal cord
- A48.7 Insertion of neurostimulator electrodes into the spinal cord

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic literature review was not performed to identify relevant resource data in England. Data were sourced from published economic evaluations and where appropriate costs were inflated to 2016 using inflation indices from Curtis and Burns 2016 (44).

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

The applicability of the resources used in the model were assessed by the following advisors and were deemed relevant:

[redacted]

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

The list price for HF10™ therapy is [redacted] However, it should be noted that the NHS would always receive a discounted price, owing to local tender arrangements at individual Trusts or procurement hubs, or using the nationally available NHS Supply Chain catalogue price.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The list price of HF10™ therapy is not paid by any NHS Trust due to the way devices are purchased via the NHS Supply Chain catalogue (accruing significant discounts for the NHS) or using locally tendered contracts to secure additional discount for a commitment to purchase a certain volume from a manufacturer. Consequently, it is inappropriate to use the list price for

the purpose of this submission. In addition, comparator list prices are not publicly available which means a like-for-like cost comparison is not possible.

In this submission, we have opted to use UK prices which are published and referenced in peer-reviewed journals for both HF10™ therapy and TNR-SCS and TR-SCS. Prices have been inflated using accepted methodology (PSSRU Pay and Prices Index) using the base year 2007/08 for TNR-SCS and TR-SCS from Taylor et al. (2010) and the base year 2009/10 for HF10™ therapy from Annemans et al. (2014) (Table 51).

Some NHS Trusts run local tenders to secure additional discounts and a better price than NHS Supply Chain based on contractual volume commitments over a number of years. It should be noted, that some larger NHS trusts are locked into multi-year tender contracts with guaranteed volumes and will be paying less than the NHS Supply Chain price. However, it is not considered reasonable to use the lowest acquisition cost of HF10™ therapy for economic modelling, hence the cost is as proposed in the base case (UK published prices).

In a separate analysis the commercial in confidence NHS Supply Chain catalogue price for HF10™ therapy [redacted] is used as an alternative to the published and subsequently inflated HF10™ therapy cost (£16,648). It should be noted that a publicly available NHS Supply Chain price is not available for TNR-SCS and TR-SCS, therefore the inflated costs from Taylor et al. (2010) are used in this analysis for these devices. It should also be noted that any hospital can order direct from the NHS Supply Chain catalogue at the price stated above [redacted] for HF10™ therapy, irrespective of volume ordered and in the absence of a contractual commitment to any volume.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in Table 45.

Table 51: Cost variables included in the cost model

Model parameter	Base case value (95% CI)	Source
SCS trial	£5,281 (£3,441 to £7,931)	Taylor et al. (2010) inflated to 2016 (37)
Failed SCS trial (electrode removal)	£2,140 (£921 to £3,593)	Taylor et al. (2010) inflated to 2016 (37)
Permanent SCS implantation		
HF10™ therapy	£16,648 (£13,116 to £21,421)†	Annemans et al. (2014) inflated to 2016 (31)
TNR-SCS	£11,281 (£8,888 to £14,516)	Taylor et al. (2010) inflated to 2016 (37)
TR-SCS	£17,422 (£13,726 to £22,418)†	Taylor et al. (2010) inflated to 2016 (37)
SCS explantation	£2,140 (£0 to £3,015)	Taylor et al. (2010) inflated to 2016 (37)
SCS related complication	£740 (£241 to £1,869)	Taylor et al. (2010) inflated to 2016 (37)
Drug pain therapy - CMM alone (6 months)	£3,167 (£0 to £8,412)	Taylor et al. (2010) inflated to 2016 (37)
Non-drug pain therapy - CMM alone (6 months)	£956 (£0 to £1,157)	Taylor et al. (2010) inflated to 2016 (37)

Drug pain therapy - SCS + CMM (6 months)	£2,012 (£0 to 8,412)	Taylor et al. (2010) inflated to 2016 (37)
Non-drug pain therapy - SCS + CMM	£33 (£0 to £40)	Taylor et al. (2010) inflated to 2016 (37)

Abbreviations: CI, confidence interval; CMM, conventional medical management; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
† No CI data available therefore this analysis assumes the same proportional difference as reported for TNR-SCS as reported by Taylor et al (2010) (37).

In the base case the cost of SCS reimplantation for TNR-SCS, TR-SCS and HF10™ therapy is assumed to be the same as the permanent implantation cost.

However, Taylor et al. (2010) reports a lower cost for an SCS reimplantation for both TR-SCS and TNR-SCS systems than a permanent implantation, although it is not specified what the difference is associated with which limits the generalisability of the assumption to this analysis (37). An additional analysis has been performed utilising a decrement from the permanent implantation costs for SCS reimplantation costs for all systems (Table 52).

In this analysis, the permanent implantation cost of TR-SCS is also conservatively reduced to equal that of the HF10™ therapy for both permanent implantation and reimplantation.

Table 52: Alternative system cost scenario

Model parameter	Base case value	Source
Permanent SCS implantation		
HF10™ therapy	£16,648†	Annemans et al. (2014) inflated to 2016 (31)
TNR-SCS	£11,281	Taylor et al. (2010) inflated to 2016 (37)
TR-SCS	£16,648	Conservatively assumed to be equal to HF10™ therapy
SCS reimplantation		
HF10™ therapy	£14,201	Annemans et al. (2014) inflated to 2016 (31)†. Proportionally reduced to reflect the cost differential between initial and replacement systems for TR-SCS reported in Taylor et al. (2010) (4)
TNR-SCS	£10,499	Taylor et al. (2010) inflated to 2016‡ (37)
TR-SCS	£14,201	Conservatively assumed to be equal to HF10™ therapy

Abbreviations: CI, confidence interval; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

Health state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented. The health states should refer to the states in

section 9.1.7. Provide a rationale for the choice of values used in the cost model.

The analysis conservatively assumes that the cost of CMM is the same irrespective of the pain response achieved, as per previous economic evaluations. The costs used in the cost model are outlined in Table 51.

Adverse-event costs

9.3.9 Complete details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The costs used in the cost model are outlined in outlined in Table 51.

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Opioid reduction

Superior pain relief with HF10™ therapy versus traditional low-frequency SCS is likely to reduce concomitant opioid medication. This cost saving has been conservatively excluded from the cost analysis.

Paraesthesia-free

As HF10™ therapy is paraesthesia-free, it removes a potentially time-consuming step in the operating theatre. Therefore surgical procedure time is more predicatble than traditional low frequency SCS. This potential cost saving has been excluded from the cost analysis, which is likely to be a conservative assumption.

Clinic visits

Given the superior long-term outcomes of HF10™ therapy (section B), the use of HF10™ therapy could potentially allow for more efficient service configuration required for the follow-up of patients (i.e. clinic visits). This potential cost saving has been excluded from the cost analysis.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

The uncertainty around structural assumptions has been investigated:

a) Timepoints – Efficacy assessed at different timepoints in the decision tree (3, 6 and 12 months) to reflect timepoints reported in the SENZA-RCT

b) Clinical efficacy – Assessed as leg pain but also assessed as back pain

In scenario analysis, 2017/2018 tariff costs were used instead of the Taylor et al. (2010) inflated costs.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Yes, deterministic and probabilistic (PSA) sensitivity analysis were undertaken. All parameters were varied within confidence intervals (CIs). Univariate results are presented as a tornado diagram.

9.4.3 Complete the following tables as appropriate to summarise the variables used in the sensitivity analysis.

All base case values and associated CIs have been provided previously in Table 50. All probabilities (e.g. SCS trial success, proportion of patients achieving optimal pain relief etc.) were varied using a beta distribution, all costs and device longevity were varied using a gamma distribution.

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

N/A.

9.5 *Results of de novo cost analysis*

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in Table 53.

Base case results are presented in Table 53. The figures presented throughout this section reflect those in the Excel® model but the sum of the constituents may not add up exactly due to rounding.

Table 53: Base case results

	Total cost per patient	Cost saving with HF10™ therapy
HF10™ therapy + CMM	£87,400	-
TNR-SCS + CMM	£95,156	£7,755
TR-SCS + CMM	£92,196	£4,795

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

Results are also presented using the commercial in confidence NHS Supply Chain price which is nationally available for HF10™ therapy (Table 54), demonstrating that HF10™ therapy is cost saving compared to TNR-SCS and TR-SCS.

Table 54: Results using nationally available NHS Supply Chain price for HF10™ therapy

	Total cost per patient	Cost saving with HF10™ therapy
HF10™ therapy + CMM	[redacted]	[redacted]
TNR-SCS + CMM	[redacted]	[redacted]
TR-SCS + CMM	[redacted]	[redacted]

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

A cost utility analysis was also conducted utilising the same utility estimates reported in NICE TAG159, results for HF10™ therapy are reported in section 9.5.12.

9.5.2 Report the total difference in costs between the technology and comparator(s).

HF10™ therapy would result in cost savings of £7,775 per patient compared to TNR-SCS and £4,795 per patient compared to TR-SCS.

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in Table 55.

A summary of costs by category of cost per patient is provided in Table 55 and Table 56.

Table 55: Summary of costs by category of cost per patient: HF10™ therapy versus TNR-SCS

Health state	HF10™ therapy	TNR-SCS	Increment	Absolute increment	% absolute increment
Initial trial	£5,281	£5,281	£0	£0	0%
Permanent implant (successful trial)	£15,449	£9,928	£5,522	£5,522	29%
Explant (failed trial)	£154	£257	-£103	£103	1%
Pain management and complication costs	£58,150	£63,588	-£5,439	£5,439	29%
Reimplantation	£7,120	£14,479	-£7,359	£7,359	39%
Explant	£624	£739	-£114	£114	1%
Revision	£621	£884	-£262	£262	1%
Total	**£87,400**	**£95,156**	**-£7,755**	**£18,799**	**100%**

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation.

Table 56: Summary of costs by category of cost per patient: HF10™ therapy versus TR-SCS

Health state	HF10™ therapy	TR-SCS	Increment	Absolute increment	% absolute increment
Initial trial	£5,281	£5,281	£0	£0	0%
Permanent implant (successful trial)	£15,449	£15,332	£118	£118	2%
Explant (failed trial)	£154	£257	-£103	£103	2%
Pain management and complication costs	£58,150	£63,477	-£5,328	£5,328	78%
Reimplantation	£7,120	£6,226	£894	£894	13%
Explant	£624	£739	-£114	£114	2%
Revision	£621	£884	-£262	£262	4%
Total	**£87,400**	**£92,196**	**-£4,795**	**£6,819**	**100%**

Abbreviations: TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in Table 57.

A summary of costs by health state per patient are provided in Table 57 and Table 58.

Table 57: Summary of costs by health state per patient: HF10™ therapy versus TNR-SCS

Health state	HF10™ therapy	TNR-SCS	Increment	Absolute increment	% absolute increment
Optimal pain relief w/o comp	£29,588†	£19,176	£10,411	£10,411	40%
Optimal pain relief w comp	£1,180	£1,457	-£278	£278	1%
Sub-optimal pain relief w/o comp	£27,103	£41,733	-£14,629	£14,629	56%
Sub-optimal pain relief w comp	£279	£1,222	-£943	£943	4%
Total	**£58,150**	**£63,588**	**-£5,439**	**£26,262**	**100%**

Abbreviations: Comp, complications; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; w, with; w/o, without.

† This cost is initially higher for HF10™ therapy as more patients achieve optimal pain relief and go on to full implant versus TNR-SCS and TR-SCS (higher responder rate from SENZA-RCT).

Table 58: Summary of costs by health state per patient: HF10™ therapy versus TR-SCS

Health state	HF10™ therapy	TR-SCS	Increment	Absolute increment	% absolute increment
Optimal pain relief w/o comp	£29,588†	£19,343	£10,244	£10,244	40%
Optimal pain relief w comp	£1,180	£1,230	-£50	£50	0%
Sub-optimal pain relief w/o comp	£27,103	£41,873	-£14,769	£14,769	57%
Sub-optimal pain relief w comp	£279	£1,031	-£752	£752	3%
Total	**£58,150**	**£63,477**	**-£5,328**	**£25,817**	**100%**

Abbreviations: Comp, complications; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation; w, with; w/o, without.

† This cost is initially higher for HF10™ therapy as more patients achieve optimal pain relief and go on to full implant versus TNR-SCS and TR-SCS (higher responder rate from SENZA-RCT).

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in Table 59.

A summary of costs by adverse events per patient are provided in Table 59 and Table 60.

Table 59: Summary of costs by adverse events per patient: HF10™ therapy versus TNR-SCS

Adverse event	HF10™ therapy	TNR-SCS	Increment
Device-related complication	£387	£712	£324
Total	**£387**	**£712**	**£324**

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation.

Table 60: Summary of costs by adverse events per patient: HF10™ therapy versus TR-SCS

Adverse event	HF10™ therapy	TR-SCS	Increment
Device-related complication	£387	£600	£213
Total	**£387**	**£600**	**£213**

Abbreviations: TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables.

Univariate sensitivity analysis

Results of the univariate sensitivity analysis for HF10™ versus TNR-SCS are provided in Table 61, a tornado diagram is also provided

† HF10™ therapy not cost saving.

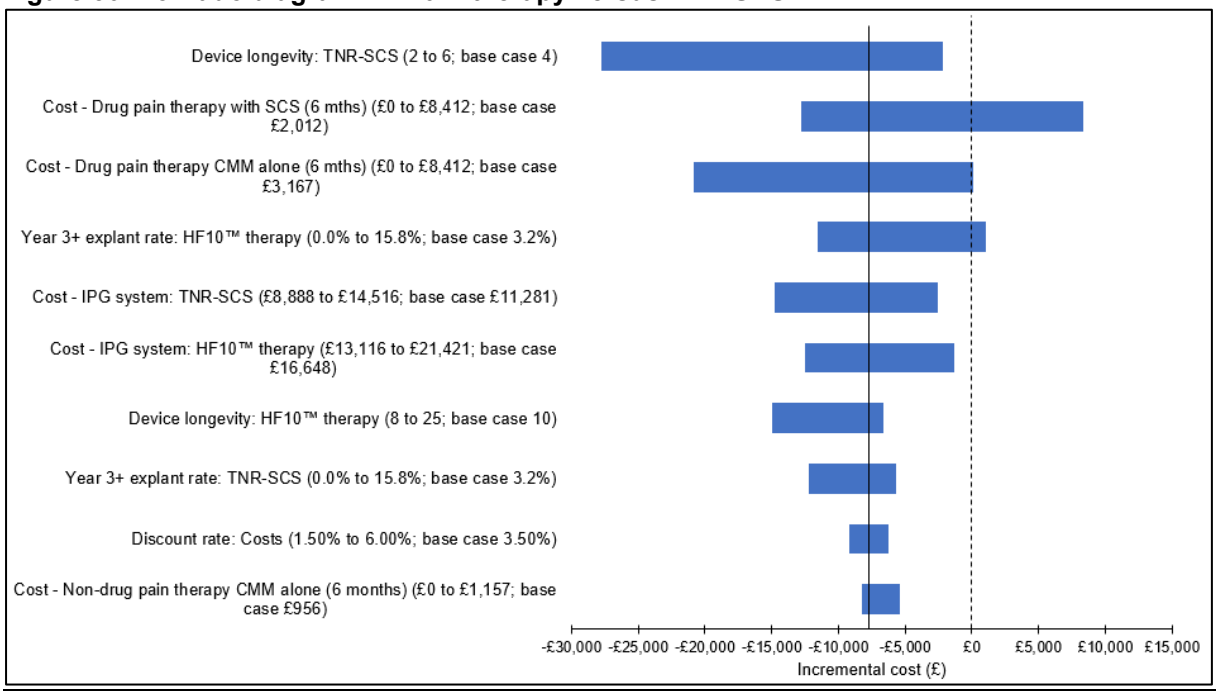
Figure 30).

Table 61: Results of univariate analysis: HF10™ therapy versus TNR-SCS

Variable (Low value to high value; base case value)	Cost differential per patient with low value	Cost differential per patient with high value
Device longevity: TNR-SCS (2 to 6; base case 4)	-£27,776.35	-£2,129.89
Cost - Drug pain therapy with SCS (6 mths) (£0 to £8,412; base case £2,012)	-£12,812.52	£8,333.83
Cost - Drug pain therapy CMM alone (6 mths) (£0 to £8,412; base case £3,167)	£122.58	-£20,799.36
Year 3+ explant rate: HF10™ therapy (0.0% to 15.8%; base case 3.2%)	-£11,510.27	£1,078.51
Cost - IPG system: TNR-SCS (£8,888 to £14,516; base case £11,281)	-£2,577.41	-£14,753.35
Cost - IPG system: HF10™ therapy (£13,116 to £21,421; base case £16,648)	-£12,543.44	-£1,284.05
Device longevity: HF10™ therapy (8 to 25; base case 10)	-£6,593.75	-£14,926.87
Year 3+ explant rate: TNR-SCS (0.0% to 15.8%; base case 3.2%)	-£5,675.17	-£12,194.30
Discount rate: Costs (1.50% to 6.00%; base case 3.50%)	-£9,216.13	-£6,230.55
Cost - Non-drug pain therapy CMM alone (6 months) (£0 to £1,157; base case £956)	-£5,377.75	-£8,255.07

Abbreviations: CMM, conventional medical management; TNR-SCS, traditional low-frequency non-rechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
Note: All model parameters were assessed but only the top ten drivers of cost are shown.
† HF10™ therapy not cost saving.

Figure 30: Tornado diagram: HF10™ therapy versus TNR-SCS



Abbreviations: CMM, conventional medical management; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
Note: All model parameters were assessed but only the top ten drivers of cost are shown.

The top three drivers of cost are:

- The device longevity of the TNR-SCS device
- Drug pain therapy cost associated with CMM when given in combination with SCS
- Drug pain therapy cost associated with CMM alone (not given in combination with SCS)

The following values result in an incremental cost for HF10™ therapy:

- The highest drug pain therapy cost associated with CMM when given in combination with SCS
- The highest drug pain therapy cost associated with CMM when given alone
- The highest explant rate from year 3 onwards for HF10™ therapy

The drug pain therapy cost associated with HF10™ therapy are likely to be lower than that of TR-SCS as superior pain relief with HF10™ therapy is likely to reduce concomitant opioid medication. This cost saving has been conservatively excluded from the cost analysis.

[redacted] The model considers the explant rate independently for HF10™ therapy, TNR-SCS and TR-SCS however, there is nothing to suggest that that the extreme figure resulting in a small incremental cost for HF10™ therapy would be seen in reality.

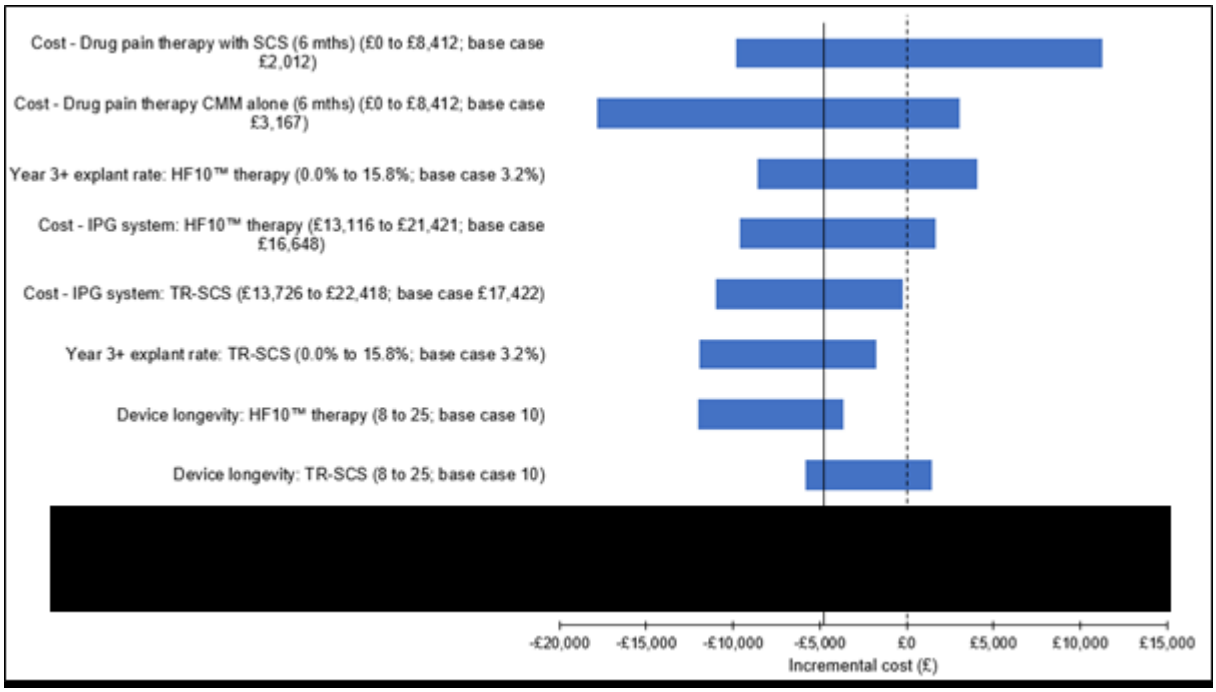
Results of the univariate sensitivity analysis for HF10™ therapy versus TR-SCS are provided in Table 62, a tornado diagram is also provided (Figure 31).

Table 62: Results of univariate analysis: HF10™ therapy versus TR-SCS (Contains AiC)

Variable (Low value to high value; base case value)	Cost differential per patient with low value	Cost differential per patient with high value
Cost - Drug pain therapy with SCS (6 mths) (£0 to £8,412; base case £2,012)	-£9,852.59	£11,293.76†
Cost - Drug pain therapy CMM alone (6 mths) (£0 to £8,412; base case £3,167)	£3,082.51†	-£17,839.43
Year 3+ explant rate: HF10™ therapy (0.0% to 15.8%; base case 3.2%)	-£8,550.34	£4,038.44†
Cost - IPG system: HF10™ therapy (£13,116 to £21,421; base case £16,648)	-£9,583.51	£1,675.88†
Cost - IPG system: TR-SCS (£13,726 to £22,418; base case £17,422)	-£221.87	-£10,976.59
Year 3+ explant rate: TR-SCS (0.0% to 15.8%; base case 3.2%)	-£1,780.71	-£11,896.38
Device longevity: HF10™ therapy (8 to 25; base case 10)	-£3,633.82	-£11,966.94
Device longevity: TR-SCS (8 to 25; base case 10)	-£5,810.78	£1,473.72†
Year 1 explant rate: TR-SCS [redacted]	[redacted]	[redacted]
Year 2 explant rate: TR-SCS [redacted]	[redacted]	[redacted]

Abbreviations: CMM, conventional medical management; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
Note: All model parameters were assessed but only the top ten drivers of cost are shown.
† HF10™ therapy not cost saving.

Figure 31: Results of univariate analysis: HF10™ therapy versus TR-SCS (Contains AiC)



Abbreviations: CMM, conventional medical management; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
Note: All model parameters were assessed but only the top ten drivers of cost are shown.

The top three drivers of cost are:

- Drug pain therapy cost associated with CMM when given in combination with SCS
- Drug pain therapy cost associated with CMM alone (not given in combination with SCS)
- The explant rate from year 3 onwards for HF10™ therapy

The following values result in an incremental cost for HF10™ therapy:

- The highest drug pain therapy cost associated with CMM when given in combination with SCS
- The lowest drug pain therapy cost associated with CMM alone
- Highest explant rate from year 3 onwards for HF10™ therapy
- Highest device implantation cost for HF10™ therapy
- Highest device longevity for TR-SCS systems

As previously noted the drug pain therapy costs associated with HF10™ therapy are likely to be lower than TNR-SCS. Similarly, the explant rate from year 3 onwards is unreflective of the trial data which shows a much lower explant rate for HF10™ therapy. The highest device longevity for TR-SCS is assumed to be 25 years, this is more than double the baseline figure. In addition, this is based on engineering tests, and engineering tests suggest the same figure for HF10™ therapy. Therefore, there is no difference between HF10™ therapy and TR-SCS systems.

Threshold analysis

Threshold analysis has been performed on the top 10 model parameters, as identified in the univariate sensitivity analysis above, to determine at which values HF10™ therapy would be cost neutral compared to TNR-SCS (Table 63) and TR-SCS (Table 64). In this analysis, all other parameters are kept at their original value.

Table 63: Results of threshold analysis for HF10™ therapy versus TNR-SCS

Variable	Base case (CI: lower – upper or range)	Cost neutral value
Device longevity: TNR-SCS	4 (2 to 6)	7.5‡
Cost - Drug pain therapy with SCS (6 mths)	£2,012 (£0 to £8,412)	£5,097
Cost - Drug pain therapy CMM alone (6 mths)	£3,167 (£0 to £8,412)	£49
Year 3+ explant rate: HF10™ therapy	3.2% (0.0% to 15.8%)	13.6%
Cost - IPG system: TNR-SCS	£11,281 (£8,888 to £14,516)	£7,697
Cost - IPG system: HF10™ therapy	£16,648 (£13,116 to £21,421)	£22,368
Device longevity: HF10™ therapy	10 (8 to 25)	NA
Year 3+ explant rate: TNR-SCS	3.2% (0.0% to 15.8%)	-5.9%†
Discount rate: Costs	3.50% (1.50% to 6.00%)	26.04%

Cost - Non-drug pain therapy CMM alone (6 months)	£956 (£0 to £1,157)	-£2,162†

Abbreviations: CMM, conventional medical management; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
†These values are negative and would not occur in reality i.e. they are outside a plausible range.
‡ These values are not the values for cost-neutrality. Due to the quarterly cycle length it is not possible to have a zero cost difference. The figures reported indicate the point at which HF10™ therapy is more costly.

In the threshold analysis when parameters are considered individually, in order for HF10™ therapy to be cost neutral compared to TNR-SCS:

- The device longevity for TNR-SCS system is greater than 7.5 years which is outside of the plausible range presented.
- The cost of the drug pain therapy element of CMM given with SCS would need to be more than double the cost (£5,097)
- The explant rate for the HF10™ system would need to be 13.6% in year 3 onwards
- The following costs would need to be negative which is impossible:
    - Drug pain therapy element of CMM given alone
    - Explant rate for the TNR-SCS system in year 3 onwards
- The cost of HF10™ therapy system would need to increase to £22,368 or the cost of the TNR-SCS system would need to drop to £7,697 (which is below the lower CI defined).

No device longevity figures could be identified for HF10™ therapy or TNR-SCS that would result in cost-neutrality.

Table 64: Results of threshold analysis for HF10™ therapy versus TR-SCS (Contains AiC)

Variable	Base case (CI: lower – upper or range)	Cost neutral value
Cost - Drug pain therapy with SCS (6 mths)	£2,012 (£0 to £8,412)	£3,919
Cost - Drug pain therapy CMM alone (6 mths)	£3,167 (£0 to £8,412)	£1,239
Year 3+ explant rate: HF10™ therapy	3.2% (0.0% to 15.8%)	8.8%
Cost - IPG system: HF10™ therapy	£16,648 (£13,116 to £21,421)	£20,185
Cost - IPG system: TR-SCS	£17,422 (£13,726 to £22,418)	£13,547
Year 3+ explant rate: TR-SCS	3.2% (0.0% to 15.8%)	-1.6%†
Device longevity: HF10™ therapy	10 (8 to 25)	6.75‡
Device longevity: TR-SCS	10 (8 to 25)	15.25‡
Year 1 explant rate: TR-SCS	[redacted]	[redacted]
Year 2 explant rate: TR-SCS	[redacted]	[redacted]

Abbreviations: CMM, conventional medical management; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
†These values are negative and would not occur in reality i.e. they are outside a plausible range.
‡ These values are not the values for cost-neutrality. Due to the quarterly cycle length, it is not possible to have a zero cost difference. The figures reported indicate the point at which HF10™ therapy is more costly.

In this analysis when parameters are considered individually, in order for the HF10™ therapy to be more costly:

- The cost of the drug pain therapy element of CMM given with SCS would need to increase to £3,919
- The annual explant rate for HF10™ therapy for year 3 onwards would need to more than double to 8.8%
- The cost of HF10™ therapy device implantation would need to increase to £20,185 or the cost of the TR-SCS device implantation would need to drop to £13,547
- The explant rate for TR-SCS system would need to be negative in year 1, 2 and 3 years onwards, which is impossible
- The device longevity for HF10™ therapy would need to drop below 6.75 years which is lower than defined plausible range or the device longevity for TR-SCS would need to increase above 15.25 years.

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis

Back pain response

To be consistent with the model used in NICE TAG159 in the base case analysis pain relief is assessed using leg pain response, from the SENZA-RCT (19). The SENZA-RCT also reports pain relief assessed using back pain response (primary endpoint). The values for efficacy that populate the decision tree element of the model when utilising pain relief assessed as back pain response rather than leg pain response are outlined in Table 65.

Table 65: Alternative variables for the decision tree: Pain relief assessed as back pain response (Contains AiC)

Model parameter	Base case value	Source
Optimal pain relief (back pain, 6 months)		
HF10™ therapy	76.4%	Kapural et al. (2015) (19)
TNR-SCS/TR-SCS	51.9%	Kapural et al. (2015) (19)
Calculated values from the SENZA-RCT		
Optimal pain relief without complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT
TNR-SCS/TR-SCS	[redacted]	Calculated from SENZA-RCT
Optimal pain relief with complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT
TNR-SCS/TR-SCS	[redacted]	Calculated from SENZA-RCT
Sub-optimal pain relief without complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT

TNR-SCS/TR-SCS	[redacted]	Calculated from SENZA-RCT
Sub-optimal pain relief with complications		
HF10™ therapy	[redacted]	Calculated from SENZA-RCT
TNR-SCS/TR-SCS	[redacted]	Calculated from SENZA-RCT

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

Table 66: Results of scenario using back pain response as alternative to leg pain response from SENZA-RCT

	Total cost per patient	Cost saving with HF10™ therapy
HF10™ therapy	£87,400	-
TNR-SCS	£95,156	£7,755
TR-SCS	£92,196	£4,795

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

As it is assumed there is no differential between HF10™ therapy and TNR-SCS/TR-SCS for the costs of optimal and sub-optimal pain relief, the use of an alternative measure of efficacy has no impact on the cost saving. Fewer patients will reach optimal pain relief when assessed via back pain response however, HF10™ therapy still results in cost savings and more patients have optimal pain relief compared to TNR-SCS/TR-SCS.

Pain relief assessed at 3, 12 and 24 months

Again, for consistency with the NICE TAG159 model, in the base case analysis pain relief was assessed at 6-months using data from the SENZA-RCT (19). However, pain relief assessment was also repeated at 3 and 12 months in the original NICE TAG159 model, and at 24 months in the SENZA-RCT (Kapural et al. [2016]) (20). A scenario analysis was conducted to consider the impact of assessing pain relief at 3, 12 and 24 months (Table 67). Minor modifications were made to the current model; amending the decision tree to reflect either 3, 12 or 24 months and modifying the Markov section to allow entry at the appropriate associated time points.

Table 67: Alternative variables for the decision tree: Pain relief assessed at 3, 12 and 24 months

Model parameter	Base case value	Source
Optimal pain relief (leg pain, 3 months)		
HF10™ therapy	83.1%	Kapural et al. (2015) (19)
TNR-SCS/TR-SCS	55.0%	Kapural et al. (2015) (19)
Optimal pain relief (leg pain, 12 months)		
HF10™ therapy	78.7%	Kapural et al. (2015) (19)
TNR-SCS/TR-SCS	51.3%	Kapural et al. (2015) (19)
Optimal pain relief (leg pain, 24 months)		
HF10™ therapy	72.9%	Kapural et al. (2016) (20)
TNR-SCS/TR-SCS	49.3%	Kapural et al. (2016) (20)

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

The relatively small changes in efficacy over time result in only small changes in the cost differentials (Table 68).

Table 68: Results of scenario using pain relief assessment at 3, 12 and 24 months

	Total cost per patient	Cost saving with HF10™ therapy
3 months		
HF10™ therapy	£87,426	-
TNR-SCS	£95,158	£7,732
TR-SCS	£92,282	£4,856
12 months		
HF10™ therapy	£87,390	-
TNR-SCS	£95,182	£7,793
TR-SCS	£92,050	£4,661
24 months		
HF10™ therapy	£87,544	-
TNR-SCS	£95,448	£7,904
TR-SCS	£91,961	£4,418

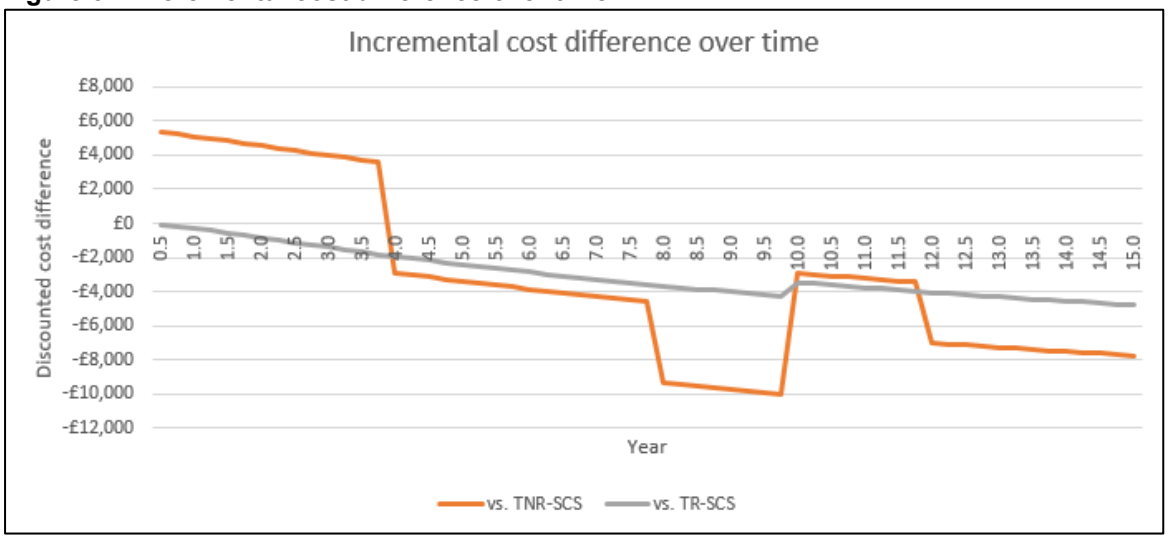
Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

Time horizon

For consistency with the model and assumptions accepted by NICE for TAG159, the base case analysis utilises a 15-year time horizon. It is felt this is appropriate in the base case given the chronic nature of the condition and the longevity of the devices, particularly those utilising a rechargeable battery. The Markov model structure allows us to present the incremental cost at various time-points as shown in Figure 32. In the base case analysis, the HF10™ therapy implantation cost is marginally cheaper than TR-SCS and therefore HF10™ therapy is cost-saving from the start of the analysis, additional cost-savings are realised over time due to the superior explant rates associated with HF10™ therapy.

Obviously, the TNR-SCS implantation cost is less than HF10™ therapy, therefore TNR-SCS remains less costly until the first TNR-SCS device replacement. After this point HF10™ therapy is cost saving.

Figure 32: Incremental cost difference over time



Abbreviations: : TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

Alternative system costs

As discussed in 9.3.7, the cost of reimplantation for TNR-SCS and TR-SCS is assumed to be lower than the cost of permanent implantation in the Taylor et al. (2010) (37) analysis. Table 69 presents the results utilising the alternative costs presented in Table 52 for reimplantation. In this analysis, the cost of reimplantation is assumed to be marginally cheaper than the cost of permanent implantation and the permanent implantation cost of TR-SCS is conservatively assumed to be equal to HF10™ therapy.

Table 69: Alternative system cost results

	Total cost per patient	Cost saving with HF10™ therapy
HF10™ therapy	£86,354	-
TNR-SCS	£94,152	£7,798
TR-SCS	£90,363	£4,009

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

This analysis results in slightly lower absolute costs due to the reduction in reimplantation costs, HF10™ therapy still remains cost saving, even with the conservative assumption of the permanent implantation cost of TR-SCS being equal to HF10™ therapy.

9.5.8 An alternative scenario is considered using the NHS tariff prices for all surgical procedures. In this scenario the costs of the devices and of CMM are based on the inflated Taylor et al. (2010) values.

The base case analysis uses inflated costs from Taylor et al. (2010) (37). However, certain costs can be replaced with NHS national tariff prices (2017/18) (Table 70). A scenario analysis was conducted to assess the impact of using these alternative costs.

Table 70: NHS national tariff prices 2017/18

Variable	Input	Reference
Cost - SCS screening trial	£2,182	OPCS code: A48.7 (Insertion of neurostimulator electrodes adjacent to the spinal cord) => HRG Code: AB14Z
Cost - Device implantation	£2,509	OPCS code A48.3 (Insertion of neurostimulator adjacent to spinal cord) => HRG Code: AB12Z
Cost - Failed screening electrode removal	£2,182	OPCS code: A48.6 (Removal of neurostimulator adjacent to the spinal cord) => HRG Code: AA54C
Cost - Device explantation	£2,182	OPCS code: A48.6 (Removal of neurostimulator adjacent to the spinal cord) => HRG Code: AA54C
Cost - Device-related complication	£512.50	Average of: OPCS code: A48.5 (Reprogramming of neurostimulator adjacent to spinal cord) => HRG Code: AA55C (£440) and OPCS code: A48.4 (Attention to neurostimulator adjacent to spinal cord) => HRG Code: AA57A (£585)

Abbreviations: HRG, healthcare resources group; OPCS: office of population censuses and surveys; SCS, spinal cord stimulation.

Table 71: Results of scenario analysis using alternative NHS national tariff prices

	Total cost per patient	Cost saving with HF10™ therapy
HF10™ therapy + CMM	£87,599	-
TNR-SCS + CMM	£97,286	£9,687
TR-SCS + CMM	£92,036	£4,437

Abbreviations: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

The use of the alternative NHS national reference prices instead of the inflated values reported by Taylor et al. (2010) (37) has minimal impact on the overall cost savings previously demonstrated in the base case.

9.5.9 Present results of the probabilistic sensitivity analysis

The results of the PSA were robust with HF10™ therapy remaining cost saving in 74% of simulations performed compared to TNR-SCS and 73% compared to TR-SCS. The mean cost saving was £7,170 per patient (95% CI: -£6,767 to -£7,573) versus TNR-SCS and £3,552 per patient (95% CI: -£3,313 to -£3,792) versus TR-SCS.

9.5.10 What were the main findings of each of the sensitivity analyses?

Both univariate analysis and PSA show that HF10™ therapy remains cost saving when compared to both TNR-SCS and TR-SCS. Within univariate analysis very few variables resulted in incremental costs for HF10™ therapy. The PSA showed the results to be extremely stable with more than 70% of simulations resulting in cost savings versus TNR-SCS/TR-SCS.

9.5.11 What are the key drivers of the cost results?

See section 9.5.6.

9.5.12 Describe any additional results that have not been specifically requested in this template. If none, please state.

Cost-utility analysis

The model structure outlined in this submission is based on the cost-utility model previously used to assess the cost-effectiveness of SCS for NICE TAG159. As such, a natural extension of the cost-consequence analysis is to consider the impact on quality of life. A cost utility analysis was conducted utilising the same utility estimates reported in NICE TAG159 (Table 72) (37). The cost-utility analysis results are presented in Table 71.

Table 72: Utility values

Health state	Utility
Optimal pain relief w/o comp	0.598
Optimal pain relief w comp	0.528
Sub-optimal pain relief w/o comp	0.258
Sub-optimal pain relief w comp	0.258
No perceived pain reduction	0.168

Abbreviations: Comp, complications; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; w, with; w/o, without.

Table 73: Cost-utility analysis results

	Total costs	Δ Costs vs. HF10™ therapy	Total QALYS	Δ QALYs vs. HF10™ therapy	ICER vs. HF10™ therapy
HF10™ therapy + CMM	£87,400	-	5.268	-	
TNR-SCS + CMM	£95,156	£7,755	4.352	-0.916	Dominated†
TR-SCS + CMM	£92,196	£4,795	4.355	-0.913	Dominated†

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years; TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.
† Dominated = higher costs and lower QALYs.

Having previously demonstrated that HF10™ therapy is cost-saving and results in more patients in pain relief it is unsurprising that TNR-SCS and TR-SCS are both dominated by HF10™ therapy. This analysis does not impact the base case result previously presented. However, it does highlight that if HF10™ therapy and TNR-SCS/TR-SCS were assessed in a cost-utility analysis, HF10™ therapy would dominate both TNR-SCS and TR-SCS. In addition, the uncertainty demonstrated in the sensitivity analysis sections would be further reduced in a traditional cost-utility analysis. This result is entirely consistent with the findings of a cost-

utility analysis comparing HF10™ therapy and TNR-SCS/TR-SCS published in 2014 by Annmans et al. This paper concluded that HF10™ therapy is dominant in cost effectiveness terms versus both TR and TNR traditional low frequency SCS systems (34).

9.6 *Subgroup analysis*

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified.

N/A. (See section 9.6.5)

9.6.2 Define the characteristics of patients in the subgroup(s).

N/A. (See section 9.6.5)

9.6.3 Describe how the subgroups were included in the cost analysis.

N/A. (See section 9.6.5)

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

N/A. (See section 9.6.5)

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

None of the subgroups suggested in the final scope were included, for the following reasons:

- Complex regional pain syndrome

The SENZA-RCT did not include complex regional pain syndrome patients. Therefore, data are not available to include in this submission.

- Previous back surgery / failed back surgery syndrome

Interaction analysis from the SENZA-RCT demonstrated that the difference in pain relief for patients with previous back surgery / failed back surgery syndrome versus patients without previous back surgery was not statistically significant. Therefore, results of the economic analysis would probably not be impacted.

- Chronic pain involving the limbs / chronic pain involving the back

Results from the SENZA-RCT (see section 7.6.1), demonstrated that HF10™ therapy works just as well for chronic pain of the lower limbs as it does for chronic back pain. At 24 months, HF10™ therapy provided a statistically significant mean difference in VAS pain score from baseline versus traditional low-frequency SCS for both back and leg pain. Therefore, results of the economic analysis would probably not be impacted.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The data inputs were cross-checked and the model calculations were verified by a second health economist.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Although this analysis is not a cost-utility analysis the results are consistent with those reported by Annemans et al. (2014) which concluded that HF10™ therapy is dominant compared to both TNR-SCS and TR-SCS (34).

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The key strength of this analysis is that it is based on a previous cost-effectiveness model of SCS accepted by NICE and used as the basis for the positive recommendation of SCS by NICE in TAG159 (32). This model has been updated to represent current costs to the NHS and utilises the latest evidence available from the SENZA-RCT (19, 20). This FDA approved, head-to-head trial demonstrates that HF10™ therapy has substantial improvements in pain relief and HRQoL compared to traditional low-frequency SCS for the treatment of chronic back and/or leg pain. HF10™ therapy has significantly better rates of response and degree of response which is maintained over the long-term.

We recognise there are potential limitations of the analysis. Given the lack of current long term real world data on the use of traditional low-frequency SCS, the device longevity for traditional low-frequency SCS remains uncertain. However, as shown in sensitivity analysis if the device longevity remains at 10 years for HF10™ therapy the device longevity for TR-SCS would need to more than 15 years before HF10™ therapy is no longer cost saving. Even if this occurs

HF10™ therapy will remain clinically superior in terms of pain relief and HRQoL. Reduction in surgical procedure time and opioid reduction have been excluded in the analysis due to the lack of publicly available data for HF10™ therapy and/or TNR-SCS/TR-SCS, including them would likely increase the cost advantages and further strengthen the case in favour of HF10™ therapy

In conclusion, the cost-consequence model is based on a robust model structure used in previous evaluations of SCS by NICE. The base case analysis demonstrates that HF10™ therapy is cost saving compared to TNR-SCS and TR-SCS. Despite limitations regarding a few input assumptions (device longevity and explant rates beyond year 2), extensive sensitivity analyses demonstrate that HF10™ therapy is cost saving in the majority of scenarios. As outlined in section B, HF10™ therapy is a superior alternative to traditional low-frequency SCS systems compared to TNR-SCS and TR-SCS i.e. provides better outcomes for patients and is cost saving.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Traditional low-frequency SCS systems require 'paraesthesia mapping' as part of the operation, both for the trial and during permanent implantation (section 2.2). This step is not required for HF10™ therapy because its mode of action is paraesthesia-free. Therefore, surgical procedure time could be shorter and its duration more predictable than traditional low-frequency SCS. Incorporation of costs associated with this time saving could further increase the cost advantage of HF10™ therapy.

In addition, this analysis has not included the reduced concomitant opioid medication associated with HF10™ therapy, which may in turn reduce visits to pain clinics and other clinician contacts. Taking these into account could further increase the cost advantage of HF10™ therapy.

Both these considerations suggest that the cost saving of HF10™ system could, in practice, be higher than that presented in this submission.

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10 Appendices

10.1 *Appendix 1 Search strategy for clinical evidence (section 7.1.1)*

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library**

The following databases were searched during the systematic review of clinical evidence:

- Medline (PubMed) on the 19th December 2016
- Cochrane Library (Wiley Online Library) on the 19th December 2016
- Medline In-Process (Ovid) on the 20th December 2016
- Scopus (Elsevier) on the 20th December 2016
- Embase (Elsevier) on the 22nd December 2016

The searches were limited by date 2006 to 2016, reflecting the timeframe of the existence of the sponsor as a company (Nevro Corporation, Redwood City, CA, USA).

10.1.2 The date on which the search was conducted

See section 10.1.1.

10.1.3 The date span of the search

See section 10.1.1.

10.1.4 The complete search strategy used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

PubMed Medline 01Jan2006 – 19Dec2016; Searched on 19th December 2016

	("All fields") AND "All fields"	
1	(spinal cord stimulation) AND high frequency	719
2	Filter: Humans	209
3	Filter: English	191
4	Filter: 01Jan2006-19Dec2016	**110**
5	(spinal cord stimulation) AND 10 khz	38
6	Filter: 01Jan2006-19Dec2016	**31**
7	(spinal cord stimulation) AND nevro	**2**
8	(spinal cord stimulation) AND senza	**2**

Numbers in **bold** represent results collected for title/abstract review.

The Cochrane Library 2006 – 2016; Searched on 19th December 2016

	"Title, abstract, key words" AND "All text"	

1	“spinal cord stimulation” AND “high frequency”	24
2	Limit: 2006-2016	**22**
3	“spinal cord stimulation” AND “10 khz”	13
4	Limit: 2006-2016	**13**
5	“spinal cord stimulation” AND nevro	**1**
6	“spinal cord stimulation” AND senza	**6**

Numbers in **bold** represent results collected for title/abstract review.

Ovid Medline® In-Process and other non-indexed citations 2006 – current; Searched on 20th December 2016

	“All fields” AND “All fields”	
1	spinal cord stimulation AND high frequency	21
2	Limit: 2006-current	**20**
3	spinal cord stimulation AND 10 khz	10
4	Limit: 2006-2016	**9**
5	spinal cord stimulation AND nevro	**1**
6	spinal cord stimulation AND senza	**1**

Numbers in **bold** represent results collected for title/abstract review.

Elsevier Scopus 2006 – 2016; Searched on 20th December 2016

	“Article, title, abstract, key words” AND “All fields”	
1	“spinal cord stimulation” AND “high frequency”	337
2	Limit: 2006-2016	270
3	Limit: English	261
4	Limit: Human	149
5	Exclude: Review articles	**99**
6	“spinal cord stimulation” AND “10 khz”	66
7	Limit: 2006-2016	66
8	Limit: English	61
9	Exclude: Review articles	**43**
10	“spinal cord stimulation” AND nevro	10
11	Limit: 2006-2016	9
12	Exclude: Review articles, book chapter	**7**
13	“spinal cord stimulation” AND senza	26
14	Limit: English	24
15	Exclude: Review articles, letters, book chapter	**13**

Numbers in **bold** represent results collected for title/abstract review.

Elsevier Embase 2006 – 2016; Searched on 22nd December 2016

	“All fields” AND “All fields”	
1	‘spinal cord stimulation’ AND ‘high frequency’	220
2	Limit: 2006-2016	204
3	Exclude: Conference abstracts, review articles, letters, conference reviews	**71**
4	‘spinal cord stimulation’ AND ‘10 khz’	83
5	Exclude: Conference abstracts, review articles, letters	**19**
6	‘spinal cord stimulation’ AND nevro	51
7	Exclude: Conference abstracts, review articles	**8**
8	‘spinal cord stimulation’ AND senza	35
9	Exclude: Conference abstracts, review articles	**7**

Numbers in **bold** represent results collected for title/abstract review.

10.1.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional studies were identified by hand searching the manufacturer’s internal documentation.

10.1.6 The inclusion and exclusion criteria.

Reported in section 7.2.1.

10.1.7 The data abstraction strategy.

Identified records were assessed by a reviewer to ensure satisfaction of pre-defined inclusion/exclusion criteria. Any questions regarding study inclusion were resolved by a second reviewer.

10.2 *Appendix 2: Search strategy for adverse events (section 7.7.1)*

The clinical search strategy as detailed in Appendix 1 was also used to capture adverse event data.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library**

N/A.

10.2.2 The date on which the search was conducted

N/A.

10.2.3 The date span of the search

N/A.

10.2.4 The complete search strategy used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A.

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

N/A.

10.2.6 The inclusion and exclusion criteria.

N/A.

10.2.7 The data abstraction strategy.

N/A.

10.3 *Appendix 3: Search strategy for economic evidence (section 8.1.1)*

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **EconLIT**
- **NHS Economic Evaluation Database (NHS EED)**

The following databases were searched during the systematic review of economic evidence:

- Medline (PubMed) on the 10th January 2017
- Embase (Elsevier) on the 11th January 2017
- Medline (R) In-Process (Ovid) on the 10th January 2017
- EconLIT (ProQuest) on the 11th January 2017
- NHS EED (University of York Centre for Reviews and Dissemination) on the 10th January 2017

The searches were limited by date 2006 to present day (January 2017), reflecting the timeframe of the existence of the sponsor as a company (Nevro Corp., Redwood City, CA, USA).

10.3.2 The date on which the search was conducted.

See section 10.3.1.

10.3.3 The date span of the search.

See section 10.3.1.

10.3.4 The complete search strategies used, including all the search term textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

PubMed Medline 01Jan2006 – 10Jan2017; Searched on 10th January 2017

	Terms were searched in “all fields”	
1	high frequency	535,125
2	10 khz	7,223
3	nevro	42
4	senza	179
5	hf10	59
6	or/1-5	540,902
7	spinal cord stimulation	21,635
8	6 and 7	736
9	(cost minimisation) OR cost minimisation	2,038
10	economic evaluation	88,425
11	cost benefit	89,480
12	cost utility	12,619
13	cost-effective	107,906

14	economic model	44,432
15	incremental cost-effectiveness ratio	4,311
16	quality adjusted life years	14,509
17	or/9-16	228,016
18	8 and 17	12
19	Filter: 01Jan2006-10Jan2017	**10**

Numbers in **bold** represent results collected for title/abstract review.

Elsevier Embase 2006 – 2017; Searched on 11th January 2017

	Terms were searched in "all fields"	
1	'high frequency' AND [2006-2017]/py	45,530
2	'10 khz' AND [2006-2017]/py	756
3	nevro AND [2006-2017]/py	108
4	senza AND [2006-2017]/py	168
5	hf10 AND [2006-2017]/py	117
6	or/1-5	46,364
7	'spinal cord stimulation' AND [2006-2017]/py	3,879
8	6 and 7	234
9	'cost minimisation' AND [2006-2017]/py	2,130
10	'cost minimisation' AND [2006-2017]/py	254
11	'economic evaluation' AND [2006-2017]/py	12,480
12	'cost benefit' AND [2006-2017]/py	36,014
13	'cost utility' AND [2006-2017]/py	6,686
14	'cost-effective' AND [2006-2017]/py	62,240
15	'economic model' AND [2006-2017]/py	1,726
16	'incremental cost-effectiveness ratio' AND [2006-2017]/py	5,278
17	'quality adjusted life years' AND [2006-2017]/py	7,196
18	or/9-17	109,146
19	8 and 18	**3**

Numbers in **bold** represent results collected for title/abstract review.

Ovid Medline® In-Process and other non-indexed citations 2006 – current; Searched on 10th January 2017

	Terms were searched in "all fields," limited to publication years 2006-current	
1	high frequency	6,958
2	10 khz	356
3	nevro	7
4	senza	43
5	hf10	7
6	or/1-5	7,328
7	spinal cord stimulation	345
8	6 and 7	28
9	(cost minimisation) OR cost minimisation	28
10	economic evaluation	1,274
11	cost benefit	2,416
12	cost utility	649
13	cost-effective	10,564
14	economic model	215
15	incremental cost-effectiveness ratio	721
16	quality adjusted life years	1,165
17	or/9-16	13,758
18	8 and 17	**28**

Numbers in **bold** represent results collected for title/abstract review.

ProQuest EconLIT 01Jan2006 – 11Jan2017; Searched on 11th January 2017

	Terms were searched "anywhere," limited to publication dates 01Jan2006-11Jan2017	

1	high frequency AND spinal cord stimulation	0
2	high frequency AND SCS	0
3	spinal cord stimulation	0
4	10 khz	0
5	nevro	0
6	senza	21
7	Limit: English	**3**
8	hf10 therapy	0
9	neuromodulation	**3**
10	neurostimulation	0
11	neurostimulator	0
12	neurostimulation market	0

Numbers in **bold** represent results collected for title/abstract review.

CRD NHS EED 2006 – 2017; Searched on 10th January 2017

	Terms were searched in "any field," limited to publication years 2006-2017	
1	spinal cord stimulation	9
2	spinal cord stimulation AND high frequency	0
3	spinal cord stimulation AND 10 khz	0
4	spinal cord stimulation AND nevro	0
5	spinal cord stimulation AND senza	0
6	spinal cord stimulation AND hf10	0

10.3.5 Details of any additional searches, (for example, searches of company databases [include a description of each database]).

Searches of internal Nevro company documentation did not identify any published or unpublished economic evaluation studies.

10.4 *Appendix 4: Resource identification, measurement and valuation (section 9.3.2)*

A systematic review was not conducted to identify relevant resource data from the published literature. Resource use was identified via existing published data.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- ***Medline (R) In-Process***
- ***NHS EED***
- ***EconLIT***

N/A.

10.4.2 The date on which the search was conducted.

N/A.

10.4.3 The date span of the search.

N/A.

10.4.4 The complete search strategies used, including all the search terms textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A.

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A.

10.4.6 The inclusion and exclusion criteria.

N/A.

10.4.7 The data abstraction strategy.

N/A.

11 Related procedures for evidence submission

11.1 *Cost models*

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 *Disclosure of information*

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

11.3 *Equality*

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the

technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

National Institute for Health and Care Excellence

External Assessment Centre correspondence

MT330 Senza SCS

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
N/A	22/06/2017. Initial teleconference with the company, raising EAC queries on the company submission of clinical evidence.	EAC notes of call: Appendix 1	Appendix 1: Copy of EAC questions sent to NICE on 16/06/2017, in preparation for the initial call with the company on 22/06/2017. Plus EAC notes of the discussions on that call.
N/A	06/07/2017. Email to Kieran Murphy, UK company representative, sharing notes of initial teleconference between NY EAC, NICE and the company on 22/06/2017. The EAC invited a company fact check of the notes of the call (Appendix 1 of this log) and any additional detail to inform the questions raised on the call.	20/07/2017 KM sent corrections to some names of Company attendees at the 22/06/2017 teleconference, plus other minor corrections as a fact check of the notes of the call. With regard to the invited additional detail, the company made two substantive additions to these notes of the discussions, one of which was marked up by them as Commercial in Confidence as per NICE protocol. In summary, these two additions were: [redacted]	The EAC has additionally marked the second substantive addition to the notes of the company teleconference (in Appendix 4 of this log) as Commercial in Confidence (to be redacted from the public version of this log). The reason for this is that this company opinion on the Perruchoud et al. study (2013) has no bearing on the independent EAC assessment of its relevance to the topic and no changes were made to the EAC assessment report as a result of receiving this additional detail. However, the company will have the opportunity to fact check the assessment report before

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		[redacted] 2. In question 17, some further company opinion on the Perruchoud et al. study (2013).	its implementation into the Assessment Report Overview (ARO).
N/A	10/07/2017 EAC Questions to Expert Advisers (Appendix 3) sent to: i) Alastair Jenkins ii) Karen Sanderson iii) Tim Johnson	i) Alastair Jenkins 11/07/2017 ii) Karen Sanderson 17/07/2017 iii) Tim Johnson 17/07/2017	Appendix 3: Collated responses to Questions to Expert Advisers The information provided by the Experts confirmed the EAC understanding of the topic and did not contradict the published evidence used to inform the EAC assessment report. Operational aspects such as procedure time, battery duration and NHS experience of adverse events were all within the ranges applied by the company in their economic model.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
	25/07/2017 Further questions sent to Kieran Murphy, Nevro (Appendix 5)	26/07/2017 Response from KM: Thank you for sharing your questions. We are currently working through our responses to the questions and will have something back to you as soon as we have addressed each of them. All best wishes, Kieran 26/07/2017 From HC to KM: Thank you Keiran. Would you please prioritise questions 2 and 3 and have those price breakdowns back to me as soon as possible? Questions 1 and 4 to 6 could then follow. Please also continue to 'Reply All', as we are on annual leave at different times and would not want to miss your response. Much appreciated, Helen 26/07/2017 From KM to HC: Helen, Would it be possible to have a quick call with you today/tomorrow to	Teleconference at 15:00 (Notes & Actions, Appendix 6

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		ensure we have understood the questions correctly? 30 mins late this afternoon could work or end of the day tomorrow? Thanks,Kieran HC to KM 27/07/2017 Thanks Kieran. 3pm is latest I could take a call (both days) if that suits? However, today would be preferred, in hope that we can have these answers before our Assessment Report completion deadline early next week. Alternatively, happy to carry on over email if you would like to detail which parts of the questions are not clear – particularly questions 2 and 3? In these, we are simply looking for clarification on whether the [redacted]NHS Supply Chain price quoted is for the implantable generator only, or generator plus all leads and other components	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		required (i.e. a complete system only price).And whether the £16,648 'HF10 therapy' price is also for the device/system only, or whether it includes implantation procedural costs such as costs of consultation, investigations, surgery and hospital admissions. All the best. Helen From KM to HC 27/06/2017: Could you dial in to a call at 3pm for 30 mins and run through the questions with us? [redacted] As a reminder for your communications log anything relating to Supply Chain prices is CIC and must be kept confidential Thanks, Kieran From HC to KM 27/06/2017:	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		Thanks Kieran, I can do that at 3pm. For clarification, we access the NHS Supply Chain catalogue, which lists the negotiated NHS prices (inc. VAT and delivery) for Senza, Boston Scientific, Medtronic and St Jude Medical IPGs (rechargeable and non-rechargeable), plus leads / accessories etc. These are used for reference, where relevant, in the NICE EAC assessment report and are not treated as confidential information. I note your requirement for the [redacted] figure to be kept confidential. It would be helpful to us if you could clarify which components of the Senza system this includes. I attach the Nevro/Senza information from NHS Supply Chain catalogue to this email, for your reference. This is Question 2 in our list of further questions. All the best. Helen	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
N/A	27/07/2017 Call with KM to discuss additional queries (Appendix 5)	31/07/2017 KM supplied written responses to queries discussed at call on 27/07/2017 (Appendix 6, contains CiC information) and patient level data on explantation rates (attached separately, all CiC)	

[Insert additional rows if required]

Appendix 1

MT330 Senza SCS – Questions for Nevro

T/C Thursday 22nd June 16:00-17:00

In Attendance:

Andrew Sims (AJS), Helen Cole (HC), Iain Willits (IW), Emma Belilios (EB) – NY EAC

Liesl Millar (LM), Bernice Dillon (BD) – NICE

Kieran Murphy (KM), Brad Gliner (BG), David Garaway (DG), Katherine Bock (KB) - Nevro

1) Purpose

The purpose of the call is to introduce the company to the EAC, and for the EAC to address queries on the company's clinical submission directly with the company. From now on the EAC will contact the company directly with any queries. All correspondence will be recorded in the correspondence log which will be published with the final report; therefore the company were asked to flag any information that is commercial in confidence so it can be redacted before publication.

2) Introductions

LM – Technical Analyst, NICE
BD – Technical Adviser, NICE
AJS – EAC Director, NY EAC
HC – Head of Service, NY EAC
IW – Lead author, NY EAC
EB – EAC Administrator, NY EAC

LM will send contact details to KM.

POST MEETING NOTE: Contact details sent 22/06/2017

3) Questions for Nevro from EAC

Nevro were thanked for their clinical submission, which is one of the most complete company submissions the EAC has seen. The EAC has put together a list of queries, submitted 16/06/2017. Nevro are currently working on the economic submission. As the deadline coincides with a US holiday, the intention is to submit early. Once the economic submission is completed they will have more time to provide any additional detail needed on the queries.

Background

Low frequency (LF) SCS has been in use for several decades and its mode of action, induction of paraesthesia, is relatively well understood. In contrast, high frequency (HF)

SCS is a comparatively recent advance in the field and less seems to be known about its mechanism. In this context:

1. *Could you tell us about the history of the development HF-SCS and the science behind its mechanism of action? How was the technology first hypothesised and tested?*

   BG – Nevro was founded in 2006 following a think-tank session at the Mayo clinic around high frequency stimulation in in various contexts, including pain control. The concept that high frequency stimulation at 10 kHz (HF10) delivered to the spinal dorsal root could be effective for pain control was developed. Initial (animal) studies suggested the process was safe, and an external prototype device was built. A comparative feasibility study compared traditional (low frequency) SCS with HF10. Patients underwent an initial trial to see if they were suitable for a traditional SCS implant. During the second phase, patients were given investigational stimulation at 10 kHz (HF10). An unexpected finding was that HF10 was found to deliver pain relief without the paraesthesia associated with traditional SCS. This led to the development of an implantable HF10 SCS system. A prospective case study in Europe was extended from 6 months to 24 months, and showed positive results both in terms of response rate and pain relief (back and leg). Senza SCS received a CE mark in 2010.

   A 12-month Randomised Control Trial (RCT) in the US [2] provided evidence of superiority vs. low frequency SCS and Senza SCS received FDA approval in 2015.

   Traditional SCS has been around for about 40 years, and research is still on-going as to the exact mechanism of action. It is understood that traditional SCS stimulates dorsal column fibres (causing paraesthesia) which activates inhibitory neurons which suppresses the nerves associated with pain. It is thought that high frequency SCS works differently. It appears to have a more direct effect, which avoids paraesthesia. This means the patient's relationship with the therapy is very different. With traditional SCS, patients frequently have to adjust the level of therapy which appears not to be the case for high frequency SCS.

2. *Were any pre-commercial (i.e. prototype) Senza devices developed and tested?*

   There are 2 commercial devices, NIPG 1000 (used in the European study) and the later NIPG 1500 (used in the US RCT). They are functionally the same, the 1500 has a new shape and some internal updates.

3. *Could you direct us to published literature on the mechanism of action of 10kHz frequency SCS?*

LM has provided an animal study which the Committee found helpful in understanding the mechanism of action (Cuellar et al, 2012).

4. *LF SCS requires intra-operative paraesthesia mapping to optimise pain relief, which the patient relays through feedback. HF SCS does not require this but instead uses common anatomical landmarks for lead placement. Are the mechanisms of action of LF and HF SCS therefore fundamentally different?*

   Already addressed.

5. *To your knowledge, is the frequency, amplitude (which is variable), and pulse width considered optimal? Is there any on-going research into further optimisation?*

   The current device is the optimal to date, although Nevro are always looking to improve and there is a strong team carrying out ongoing research into how the device can be optimised.

6. *Is the intellectual property of Senza technology protected? Could other companies replicate its success?*

   Nevro hold several international patents relating to the technology.

Population

The population described in the scope is clearly defined, matching the recommendations of TA159 [1] (i.e. management of chronic, severe neuropathic pain in patients recalcitrant to medical management). In this context:

7. *In your experience, what is the main underlying cause of the neuropathic pain in these patients? Is it reflected by the characteristics of patients in the Senza-RCT [2] (i.e. is this trial representative of the patients the NHS should use Senza in)?*

   KM worked on TA159 in 2006/7 (working for a different company). The TA was informed by two RCTs, the PROCESS trial [4]– comparing traditional SCS and Conventional Medical Management (CMM) with CMM only and the trial by North et al. (2015) [3], which investigated the use of LF SCS versus repeated surgery in failed back surgery syndrome. Failed back surgery syndrome (FBSS) is one cause of chronic neuropathic pain, but whether a patient has had back surgery previously is not paramount to whether SCS is a suitable treatment option. This has more to do with definitions around pain. The patients included in the SENZA-RCT were very similar in characteristics to those reported in the studies informing TA159.

8. *Could you describe the pathway of a "typical" patient, if there is one? That is, what combination of drugs, surgery, and other treatments might have been tried before Senza is considered?*

The population appear to be a heterogenous group – is there a 'typical' patient? Surgery might be part of the workup. From the literature, c. 85% of SCS patients have failed back surgery syndrome. However, it is not necessary for patients to have had previous back surgery to benefit. Some will have had CMM only. The spread of 85% with FBSS and 15% without surgery is most common in the UK also.

9. *Is the population exactly the same as those who could be treated with LF SCS? Or are there likely to be some patients that benefit more from either technology?*

   See 7 and 10.

10. *Would you consider Senza as a direct replacement for LF SCS or as an alternative? Would introduction of Senza displace existing technology*?

    Nevro would consider Senza SCS as superior to LF SCS, i.e., a replacement. However, it is thought that the technologies have different mechanisms of action, therefore patients that do not respond to one might benefit from the other.

Clinical research

The evidence from TA159 for the use of LF SCS in the treatment of neuropathic pain is derived from two RCTs, the trial by North et al. (2015) [3], which investigated the use of LF SCS versus repeated surgery in failed back surgery syndrome (FBSS) patients, and the PROCESS trial [4], which investigated the use of LF SCS versus continued medical management.

11. *These studies used different LF SCS devices compared with the comparator used in the Senza-RCT trial (which used the Precision Plus System [Boston Scientific]). Are you confident that LF SCS technologies perform equivalently and therefore that the results from the Senza-RCT are generalisable against all available traditional SCS systems?*

    Yes, studies have shown remarkable consistency of LF SCS systems both in terms of responder rates and pain relief, although there has never been a comprehensive comparison done, and it is unlikely this would be useful. LF SCS systems use similar frequencies are technically equivalent. Most LF SCS systems do not have RCT evidence.

12. *Both these studies were exclusive to patients with FBSS, whereas Senza-RCT recruited a mixed cohort with predominant FBSS. Are you confident these populations are generalisable with each other?*

    Yes. See response to question 8.

13. *The protocol for the Senza-RCT in clinicaltrials.gov (NCT01609972) reported that anticipated recruitment for the trial was 356. However, only 198 patients were recruited for the trial. Is there any reason for this discrepancy?*

    The discrepancy was due to the expected attrition due to eligibility criteria (that is, the sample size included patients who would be expected to be excluded following eligibility screening).

14. *There are a large number of single-armed studies published as abstracts. Are there any plans to synthesise this data as a meta-analysis?*

    No plans within the timelines of this assessment report, but it is a good idea.

15. *Are there any plans for further comparative studies, preferably RCTs, to increase the confidence of the effect and safety of treatment compared with another device or continued medical management?*

    Yes. One (UK based, Guy's hospital) looking at Senza SCS for refractory back pain in patients who have not previously had back surgery. Patients randomised to CMM or CMM plus HF10. They had subgroups like this in the Senza-RCT. Plan is to conduct this trial at Guy's with Al-Kaisy.

16. *Another application of SCS is burst stimulation (St Jude Medical). Are there any plans for comparative trials of Senza HF SCS versus Burst stimulation?*

No

<u>Studies with Sham as a comparator</u>

17. *Perruchoud et al. (2013) [5] reported a small cross-over RCT where a HF (5 KHz) Medtronic device was compared with sham treatment. The results of this study were negative, with the authors concluding "It appears that the effect of HFSCS and sham is equal and only the order in the sequence, not the nature of the treatment, seems to dictate the effect". Do you have any opinion on the reasons for the negative results of this study? Is it device or frequency specific?*

[redacted].

18. *In 2011, Nevro sponsored a cross over RCT that was to compare Senza with sham (the device turned off). This has been registered as a protocol see www.isrctn.com/ISRCTN33292457) [6]. This trial was due for completion on 13th December 2012 and no reasons have been given for abandonment. Could Nevro tell us what happened with this study and any data generated from it?*

    Difficulties arose with blinding that challenged the scientific integrity of the trial. For example, the device would normally need 30 to 45 minutes of battery recharge per day. In the sham group, with the device set to zero frequency, it won't lose charge (so subject blinding became ineffective). The trial was therefore discontinued.

Costs and model

19. *We are aware that there has been a cost-utility study already published concerning the cost effectiveness of Senza [7]. This was developed using the structure of economic model used in TA159. For the de novo economic submission, is Nevro planning to use a model similar to or based on this, or is an entirely new de novo model going to be used?*

    KM – economic model will be based on the existing study. A lot of work has already been done on this, and for consistency and ease it makes sense to build on this. The company have taken sub-groups out of the scope – IW asked if the intention for doing this was to simplify the economic model (1 scenario only consistent with TA159 population). KM – lots of scenarios will be analysed to answer the questions posed. Sub groups were removed, as there were challenges trying to fit patients into the sub groups given, and the model will not get into that level of granularity. The intention is to mirror the model NICE reviewed and accepted in 2007/08. The patient group is essentially the same, so a new approach is not warranted.

20. *We have noted that the Senza device is listed in the NHS supply chain. Will this be the basis of the device cost used in the model?*

    The issue Nevro have is that they don't see comparator costs on Supply Chain due to confidential tender process.

4) Questions for EAC from Nevro

21. DG had concerns over to what extent the mechanism of action would feature in the report. Low frequency SCS has been an accepted therapy option for 40 years, and the mechanism of action is still not completely understood. Similarly with high frequency SCS, there will be some similarities and some differences. Nevro's priority is to provide clinical evidence that the technology works while

research goes on as to how it works. IW and BD reassured him that it is the clinical evidence that is of interest for the report.

5) Next Steps

- Both NICE and the EAC had difficulty in printing the clinical submission – some pages seemed to be set to a non-standard paper size. The fix locally may mean that different page numbers are created, which would be a problem for referring to these in the various assessment reports. Could Nevro please check and resolve this when whole submission (including economic) is made? Nevro agreed to make the final submission in pdf format. This is likely to be sent to NICE on Friday 30th June, i.e. earlier than economic submission is due, since the USA office closes for 4th July holiday.
- EAC's notes from the call will be shared with Nevro for their review and correction of any inaccuracies or omissions.

References

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3. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery. 2005;56(1):98-106; discussion -7.
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6. Senza™ spinal cord stimulation system for the treatment of chronic back and leg pain in failed back surgery syndrome (FBSS) patients.
7. Annemans L, Van Buyten JP, Smith T, Al-Kaisy A. Cost effectiveness of a novel 10 kHz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS). Journal of long-term effects of medical implants. 2014;24(2-3):173-83.

Appendix 2

MT330 Senza SCS – Questions for clinical experts

Question	Expert Response
Section 1: UK clinical practice of SCS for chronic neuropathic pain of the trunk and limbs	
1. Implantation time. The company has claimed that implantation time for HF10 therapy using Senza SCS (spinal cord stimulation) is quicker than for traditional (low frequency) SCS, as paraesthesia mapping is not required. They have not provided evidence on length of procedure. **Can you please comment upon this claim? From your experience, how long does a Senza implant procedure take and how long does a low frequency implant procedure take, with paraesthesia mapping?**	
2. Which grade(s) of staff carry out the following stages of the SCS procedure? a. Device implantation b. Paraesthesia mapping (low frequency only) c. Device programming d. Follow up clinic appointments The Senza company does not think a Consultant grade needs to conduct its device programming, as, unlike conventional low frequency SCS, their programming is standardised to a limited number of optimised settings. **Can you please comment on this aspect of the procedure, from your experience?**	
3. Patient pathway. Trial evidence for patients undergoing conventional SCS or Senza HF10 therapy is largely restricted to patients with failed back syndrome surgery (FBSS), suggesting SCS implantation is usually conducted in patients who have exhausted conventional medical management (CMM)	

Question	Expert Response
options, including surgery. **Can you please advise whether most or all patients have had previous back surgery before they are referred for SCS in the NHS?**	
4. <u>What kind of imaging is used in theatre?</u> The company has claimed that Senza SCS can be implanted using pulsed fluoroscopy (rather than continuous fluoroscopy for traditional SCS, due to reduced amount of lead manipulation required because paraesthesia mapping is not required). **Please comment on the claim that with HF-10 Senza SCS therapy, the use of pulsed fluoroscopy instead of continuous fluoroscopy reduces patient and clinician radiation exposure. Could this be significant in terms of costs, and potential radiation exposure?**	
5. <u>Repeat back surgery</u> The company's economic model includes an option for repeat surgery in the CMM arm. The type of surgery is not specified. **In your experience, what is the maximum of repeated back surgical interventions that would be undertaken? What type of repeat surgery is offered and what are the chances of success in terms of reducing pain?**	
6. <u>Other clinical data variables in the economic model</u> Re-operation rates and pain relief post-surgery after re-operation are based on data from 2009. **Have back surgery techniques and post-op care changed significantly since 2009?**	
Section 2: The Senza SCS technology and comparators	
7. <u>High frequency SCS</u> The Senza HF10 system utilises high frequency (10 kHz). The company claims that Senza HF10 is unique in this aspect. **Is that correct, or are there any other high frequency devices CE marked and commercially available?**	

Question	Expert Response
8. <u>Burst SCS</u> We are aware of another technology, Burst SCS (St Jude Medical) that also provides pain relief without causing perceptible or uncomfortable paraesthesia. **Is Burst technology available and used in the NHS? If so, does it offer any potential benefits or disadvantages compared with conventional SCS or Senza HF10?**	
9. <u>Rechargeable vs non rechargeable</u> Conventional low frequency SCS is available as both rechargeable options. The latter is cheaper but requires more frequent replacement. **Are both options used, and if so, are they used in a similar proportion of patients? Other than price and replacement requirement, are there any advantages or disadvantage of each system type?**	
10. <u>Battery replacement</u> The company estimates that non-rechargeable low frequency SCS systems need replacing every 4 years on average (range 2 to 6 years). **Do you agree with this estimate?**	
11. <u>Reimplantation</u> All SCS systems will require replacement once their useful battery charge has drained. **Is replacing a device as difficult and resource consuming as original implantation? Are rechargeable and non-rechargeable devices equivalent in this regard?**	
12. <u>Adverse events</u> The incidence of adverse events is an important driver of the company's economic model. **In your experience, what are the principal short term (peri-procedural) and longer term adverse events associated with SCS? Are adverse events**	

Question	Expert Response
considered as a significant barrier for implementation? Are you aware of any differential in the number of adverse events of Senza HF10 compared with conventional SCS technologies?	
Section 3. Mechanism of action and research	
13. Double blind trials involving conventional SCS have not been historically possible because of unmasking due to induction of paraesthesia. However, as Senza HF10 does not induce paraesthesia, this no longer poses an insurmountable obstacle. **Do you think clinical research involving a sham arm would be useful?**	
14. Outcomes for SCS tend to be subjective and patient orientated (e.g. VAS pain score). **What proportion of patient response seen with these technologies do you think may be due to placebo effect?**	
Section 4: Procurement and payment	
15. The NICE adoption team has spoken to clinicians and found local variations in the process of purchasing SCS devices. The NICE External Assessment Centre (EAC) has found that these are included in the NHS Supply Chain catalogue (hyperlink may require a login). **Can you please comment on your experience of the NHS procurement process for SCS devices?**	
16. NHS Supply Chain categorises these SCS devices as rechargeable and non-rechargeable implantable pulse generators. Even within each section, the price range is quite wide between the different company offerings. **Please can you offer any insight into reasons for price differences and whether all are indicated for use in our patient population of interest (chronic neuropathic pain)?**	
17. We intend to try searching Hospital Episode Statistics (HES) for an	

Question	Expert Response
indication of the number of SCS procedures carried out annually in the NHS Our draft search strategy of potential OPCS-4 (procedure) and ICD-10 (diagnosis) coding combinations are appended to this questionnaire. **Please comment on the suitability of the suggested coding combinations and advise how the SCS procedure is coded in your Trust?**	

Appendix 3

NY EAC Questions to Senza SCS Clinical Experts 10/07/2017

Name of Expert Advisers	Job Title	Organisation	Nominated by	Ratified
Mr Alistair Jenkins	Consultant Neurosurgeon	Newcastle upon Tyne Hospitals NHS Trust	NICE	Yes
Ms Karen Sanderson	Advanced Nurse Practitioner	Guy's and St Thomas' NHS Trust	NICE	Yes
Dr Tim Johnson	Consultant in Pain Management	Salford Royal NHS Foundation Trust	NICE	Yes

Section 1: UK clinical practice of SCS for chronic neuropathic pain of the trunk and limbs

Question 1: Implantation time. The company has claimed that implantation time for HF10 therapy using Senza SCS (spinal cord stimulation) is quicker than for traditional (low frequency) SCS, as paraesthesia mapping is not required. They have not provided evidence on length of procedure.
Can you please comment upon this claim? From your experience, how long does a Senza implant procedure take and how long does a low frequency implant procedure take, with paraesthesia mapping?

Expert Adviser	Q1 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	The claim is correct. A Senza trial takes around 20-25 minutes, and that time is fairly consistent allowing accurate timing of lists. LF implants can be fast, but that involves luck: 30 mins – 2 hrs, average around 40 mins
Ms Karen Sanderson **Advanced Nurse Practitioner**	The leads are placed anatomical T9/T10 often requiring only one lead no parathesia mapping required therefore patient is sedated throughout the procedure. Average theatre time 45 -60 minutes Low frequency lead is placed and patient is woken from sedation the time is variable from 90 minutes to 150 minutes
Dr Tim Johnson **Consultant in Pain Management**	I defer to the clinical experts who have greater practical experience of implanting devices.

Question 2: Which grade(s) of staff carry out the following stages of the SCS procedure?

a. *Device implantation*
b. *Paraesthesia mapping (low frequency only)*
c. *Device programming*
d. *Follow up clinic appointments*

The Senza company does not think a Consultant grade needs to conduct its device programming, as, unlike conventional low frequency SCS, their programming is standardised to a limited number of optimised settings.
Can you please comment on this aspect of the procedure, from your experience?

Expert Adviser	Q2 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	i. Consultant or junior surgeon with cons supervision ii. Ditto iii. Nurse specialist iv. Ditto ie no difference
Ms Karen Sanderson **Advanced Nurse Practitioner**	a. Consultant trained in neuromodulation b. Consultant and Nurse/Rep c. Nurse/Rep d. Nurse/Consultant The nurse is able to do all aspects of programming for both type of frequency. The programming from high frequency requires no parathesia mapping but anatomical programming around the T9/T10 disc. The frequency and pulse width is set and amplitude is set by testing ensuring the patient feels no parathesia. For the patient and programmer this requires less time as there is no parathesia mapping. With low frequency where the patient feels parathesia the programmer spends longer ensuring the painful area is covered by parathesia which at times can be challenging especially when the lead is positional and patient requires different settings for lying sitting and standing
Dr Tim Johnson **Consultant in Pain Management**	As qu.1

Question 3: <u>Patient pathway.</u> Trial evidence for patients undergoing conventional SCS or Senza HF10 therapy is largely restricted to patients with failed back syndrome surgery (FBSS), suggesting SCS implantation is usually conducted in patients who have exhausted conventional medical management (CMM) options, including surgery.
Can you please advise whether most or all patients have had previous back surgery before they are referred for SCS in the NHS?

Expert Adviser	Q3 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	Probably 80%
Ms Karen Sanderson **Advanced Nurse Practitioner**	Yes majority of the patients referred for HF10 have had previous back surgery
Dr Tim Johnson **Consultant in Pain Management**	My experience is that there a substantial minority of patients who are implanted do not have back pain or failed back surgery syndrome. E.g. CRPS, amputations.

Question 4: <u>What kind of imaging is used in theatre?</u> The company has claimed that Senza SCS can be implanted using pulsed fluoroscopy (rather than continuous fluoroscopy for traditional SCS, due to reduced amount of lead manipulation required because paraesthesia mapping is not required).

Please comment on the claim that with HF-10 Senza SCS therapy, the use of pulsed fluoroscopy instead of continuous fluoroscopy reduces patient and clinician radiation exposure. Could this be significant in terms of costs, and potential radiation exposure?

Expert Adviser	Q4 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	Radiation dose certainly less with Senza on average
Ms Karen Sanderson **Advanced Nurse Practitioner**	I am unable to comment on potential radiation exposure as I am not an expert in radiation exposure
Dr Tim Johnson **Consultant in Pain Management**	As qu. 1

Question 5: <u>Repeat back surgery</u>
The company's economic model includes an option for repeat surgery in the CMM arm. The type of surgery is not specified.
In your experience, what is the maximum of repeated back surgical interventions that would be undertaken? What type of repeat surgery is offered and what are the chances of success in terms of reducing pain?

Expert Adviser	Q5 Response

Mr Alistair Jenkins **Consultant Neurosurgeon**	Not an appropriate question – SCS is not offered with either system instead of surgery if indicated Though a trial by North et al around 15 years ago showed SCS better than repeat surgery
Ms Karen Sanderson **Advanced Nurse Practitioner**	The research evidence and nice guidelines have influenced change in practice in spinal surgery for low back pain. On average patients undergo 3 to 5 spinal operations prior to being referred to a Pain clinic usually discectomy spinal fusion decompression and then revision. The pain is may be reduced for varying periods of time but often the back pain returns. Radiculopathy is rarely resolved with surgery. Surgery often increase pain and increase disability
Dr Tim Johnson **Consultant in Pain Management**	Back surgery is a poor treatment option for relief of back pain, particularly if repeated. Probability of success is low but I defer to surgical opinion further on this point.

Question 6: Other clinical data variables in the economic model
Re-operation rates and pain relief post-surgery after re-operation are based on data from 2009.
Have back surgery techniques and post-op care changed significantly since 2009?

Expert Adviser	Q6 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	No
Ms Karen Sanderson **Advanced Nurse Practitioner**	The research evidence and new nice guidelines have influenced change in practice in spinal surgery for low back pain.
Dr Tim Johnson **Consultant in Pain Management**	Defer to spinal surgery expertise.

Section 2: The Senza SCS technology and comparators

Question 7: <u>High frequency SCS</u>
The Senza HF10 system utilises high frequency (10 kHz). The company claims that Senza HF10 is unique in this aspect. Is that correct, or are there any other high frequency devices CE marked and commercially available?

Expert Adviser	Q7 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	None
Ms Karen Sanderson **Advanced Nurse Practitioner**	Yes Senza HF10 has RCT evidence superior back pain relief FBBS for patients with predominately back pain with good out comes. There is increasing more devices CE marked with varying frequency wave forms (burst /high density) is one study of burst study de ridder Neuro surgery 2010 but robust research evidence is required. Increasingly medical practitioners are moving to parathesia free neuro modulation.
Dr Tim Johnson **Consultant in Pain Management**	Defer to experts who are more familiar with devices available.

Question 8: <u>Burst SCS</u>
We are aware of another technology, Burst SCS (St Jude Medical) that also provides pain relief without causing perceptible or uncomfortable paraesthesia.
Is Burst technology available and used in the NHS? If so, does it offer any potential benefits or disadvantages compared with conventional SCS or Senza HF10?

Expert Adviser	Q8 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	Available and has proved effective. Used in patients who become resistant to conventional stim; most feel it is less effective than HF
Ms Karen Sanderson **Advanced Nurse Practitioner**	Larger RCT is required to evidence different waveforms for the effect for predominately back from FBSS the evidence is HF10. For some patients with neuropathic pain there is a combination of conventional and new wave forms or a combination.
Dr Tim Johnson **Consultant in Pain Management**	There is some evidence for efficacy of burst stimulation against placebo stimulation. The potential advantages are similar to those for HF10.

Question 9: Rechargeable vs non rechargeable

Conventional low frequency SCS is available as both rechargeable options. The latter is cheaper but requires more frequent replacement.

Are both options used, and if so, are they used in a similar proportion of patients? Other than price and replacement requirement, are there any advantages or disadvantage of each system type?

Expert Adviser	Q9 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	A matter of personal preference. In UK most are still fixed cell, in the US mostly rechargeable
Ms Karen Sanderson **Advanced Nurse Practitioner**	For high frequency you have to use re chargeable due to energy consumption Low frequency less energy consumption therefore majority we use non rechargeable.

Dr Tim Johnson **Consultant in Pain Management**	Defer to implanting experts

Question 10: Battery replacement

The company estimates that non-rechargeable low frequency SCS systems need replacing every 4 years on average (range 2 to 6 years).

Do you agree with this estimate?

Expert Adviser	Q10 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	Yes
Ms Karen Sanderson **Advanced Nurse Practitioner**	For low frequency for non re chargeable average 5 years. HF10 rechargeable battery currently we implanted the first group of HF10 IN 2009 and majority of patients have not required battery change. Battery life warranted 10 years
Dr Tim Johnson **Consultant in Pain Management**	Defer to implanting experts

Question 11: Reimplantation

All SCS systems will require replacement once their useful battery charge has drained.

Is replacing a device as difficult and resource consuming as original implantation? Are rechargeable and non-rechargeable devices equivalent in this regard?

Expert Adviser	Q11 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	Easy day-case procedure, around 20 mins. The original implant is a two-stage procedure – trial and permanent. Rechargeable systems should last up to 25 years.
Ms Karen Sanderson **Advanced Nurse Practitioner**	No 45 minutes to change the IPG from the pocket and replace. There is no need to change the leads. This is a day case procedure. There is no difference in surgical time for rechargeable or non-rechargeable
Dr Tim Johnson **Consultant in Pain Management**	Replacing batteries only is a lesser undertaking than the initial implantation with positioning of the electrodes.

Question 12: Adverse events

The incidence of adverse events is an important driver of the company's economic model.

In your experience, what are the principal short term (peri-procedural) and longer term adverse events associated with SCS? Are adverse events considered as a significant barrier for implementation? Are you aware of any differential in the number of adverse events of Senza HF10 compared with conventional SCS technologies?

Expert Adviser	Q12 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	The only AE I ever come across in infection. No difference in risk.
Ms Karen Sanderson **Advanced Nurse Practitioner**	The short term AE would be infection requiring removal of the system Dural tap headache Less common bleeding/nerve trauma Rare paralysis

	Patients should be informed of the risks but they are not a significant barrier. There is no differential number adverse event I am aware of between HF10 and conventional technologies.
Dr Tim Johnson **Consultant in Pain Management**	Both technologies have the same potential complications. Potential patients are often mindful of major complications and this may influence uptake of the procedure. Paraesthesia is unlikely as a complication of HF10 and the more standard placement may be technically less demanding and , therefore, safer.

Section 3. Mechanism of action and research

Question 13: Double blind trials involving conventional SCS have not been historically possible because of unmasking due to induction of paraesthesia. However, as Senza HF10 does not induce paraesthesia, this no longer poses an insurmountable obstacle.

Do you think clinical research involving a sham arm would be useful?

Expert Adviser	Q13 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	Not really. SCS seems sadly lacking in a placebo effect!
Ms Karen Sanderson **Advanced Nurse Practitioner**	Yes this is vital to evidence the effectiveness of spinal cord stimulation and the placebo effect. This should be non-commercial funded to prevent bias
Dr Tim Johnson **Consultant in Pain Management**	I consider it highly desirable for there to be properly conducted independent studies of high frequency spinal cord stimulation therapy against placebo. The mechanism of action of HF10 is poorly understood and it is perfectly tenable to suggest that a large proportion of the benefit is as a result of non-specific treatment effects such as placebo. Given the relative expense of the technique including the potential for complications it is important for NICE to understand how much of this therapy consists of placebo. The studies are likely to be possible. A study using 5KHz found no benefit and there is little reason to suspect a difference in the modes of action of these two frequencies.

Question 14: 14. Outcomes for SCS tend to be subjective and patient orientated (e.g. VAS pain score).

What proportion of patient response seen with these technologies do you think may be due to placebo effect?

Expert Adviser	Q14 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	See above – very little.
Ms Karen Sanderson **Advanced Nurse Practitioner**	Due to the multi factor nature of chronic pain this is subjective and is extremely hard to measure. As with all surgical/medical treatments there is a placebo effect. However further research is required to ensure the effect of spinal cord stimulation.
Dr Tim Johnson **Consultant in Pain Management**	It is impossible to say. A high proportion of the effect being as a result of placebo is impossible to exclude without studies to assess this specifically

Section 4: Procurement and payment

Question 15: The NICE adoption team has spoken to clinicians and found local variations in the process of purchasing SCS devices.

The NICE External Assessment Centre (EAC) has found that these are included in the NHS Supply Chain catalogue (hyperlink may require a login).

Can you please comment on your experience of the NHS procurement process for SCS devices?

Expert Adviser	Q15 Response

Mr Alistair Jenkins **Consultant Neurosurgeon**	No problems in my region
Ms Karen Sanderson **Advanced Nurse Practitioner**	The centre I work for has a contract and went through a tender process. We therefore have a clear process and system in purchasing implants through procurement. This contract ends the year and we are going to a zero cost model.
Dr Tim Johnson **Consultant in Pain Management**	Defer to implanting experts

Question 16: NHS Supply Chain categorises these SCS devices as rechargeable and non-rechargeable implantable pulse generators. Even within each section, the price range is quite wide between the different company offerings.

Please can you offer any insight into reasons for price differences and whether all are indicated for use in our patient population of interest (chronic neuropathic pain)?

Expert Adviser	Q16 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	Not sure I understand this question.
Ms Karen Sanderson **Advanced Nurse Practitioner**	I am unable to comment on the cost and the variation
Dr Tim Johnson **Consultant in Pain Management**	Defer to implanting experts

Question 17: We intend to try searching Hospital Episode Statistics (HES) for an indication of the number of SCS procedures carried out annually in the NHS

Our draft search strategy of potential OPCS-4 (procedure) and ICD-10 (diagnosis) coding combinations are appended to this questionnaire.

Please comment on the suitability of the suggested coding combinations and advise how the SCS procedure is coded in your Trust?

Expert Adviser	Q17 Response
Mr Alistair Jenkins **Consultant Neurosurgeon**	
Ms Karen Sanderson **Advanced Nurse Practitioner**	The clinical coding is not my area of expertise
Dr Tim Johnson **Consultant in Pain Management**	Defer to implanting experts

Appendix 4

MT330 Senza SCS – Questions for Nevro – COMPANY FEEDBACK
T/C Thursday 22nd June 16:00-17:00

In Attendance:
Andrew Sims (AJS), Helen Cole (HC), Iain Willits (IW), Emma Belilios (EB) – NY EAC
Liesl Millar (LM), Bernice Dillon (BD) – NICE
Kieran Murphy (KM), Brad Gliner (BG), David Caraway (DC), Katherine Neuenfeldt (KN) - Nevro

1) **Purpose**

The purpose of the call is to introduce the company to the EAC, and for the EAC to address queries on the company's clinical submission directly with the company. From now on the EAC will contact the company directly with any queries. All correspondence will be recorded in the correspondence log which will be published with the final report; therefore the company were asked to flag any information that is commercial in confidence so it can be redacted before publication.

2) **Introductions**

LM – Technical Analyst, NICE
BD – Technical Adviser, NICE
AJS – EAC Director, NY EAC
HC – Head of Service, NY EAC
IW – Lead author, NY EAC
EB – EAC Administrator, NY EAC

LM will send contact details to KM.
POST MEETING NOTE: Contact details sent 22/06/2017

3) **Questions for Nevro from EAC**

Nevro were thanked for their clinical submission, which is one of the most complete company submissions the EAC has seen. The EAC has put together a list of queries, submitted 16/06/2017. Nevro are currently working on the economic submission. As the deadline coincides with a US holiday, the intention is to submit early. Once the economic submission is completed they will have more time to provide any additional detail needed on the queries.

Background
Low frequency (LF) SCS has been in use for several decades and its mode of action, induction of paraesthesia, is relatively well understood. In contrast, high frequency (HF) SCS is a comparatively recent advance in the field and less seems to be known about its mechanism. In this context:

1. *Could you tell us about the history of the development HF-SCS and the science behind its mechanism of action? How was the technology first hypothesised and tested?*

BG – Nevro was founded in 2006 following a think-tank session at the Mayo clinic around high frequency stimulation in various contexts, including pain control. The concept that high frequency stimulation at 10 kHz (HF10) delivered to the spinal dorsal root could be effective for pain control was developed. Initial (animal) studies suggested the process was safe, and an external prototype device was built. A comparative feasibility study compared traditional (low frequency) SCS with HF10. Patients underwent an initial trial to see if they were suitable for a traditional SCS implant. During the second phase, patients were given investigational stimulation at 10 kHz (HF10). An unexpected finding was that HF10 was found to deliver pain relief without the paraesthesia associated with traditional SCS. This led to the development of an implantable HF10 SCS system. A prospective case study in Europe was extended from 6 months to 24 months, and showed positive results both in terms of response rate and pain relief (back and leg). Senza SCS received a CE mark in 2010.

A 12-month Randomised Control Trial (RCT) in the US [2] provided evidence of superiority vs. low frequency SCS and Senza SCS received FDA approval in 2015.

Traditional SCS has been around for about 40 years, and research is still on-going as to the exact mechanism of action. It is understood that traditional SCS stimulates dorsal column fibres (causing paraesthesia) which activates inhibitory neurons which suppresses the nerves associated with pain. It is thought that high frequency SCS works differently. It appears to have a more direct effect, which avoids paraesthesia. This means the patient's relationship with the therapy is very different. With traditional SCS, patients frequently have to adjust the level of therapy which appears not to be the case for high frequency SCS.

2. *Were any pre-commercial (i.e. prototype) Senza devices developed and tested?*

   There are 2 commercial devices, NIPG 1000 (used in the European study) and the later NIPG 1500 (used in the US RCT). They are functionally the same, the 1500 has a new shape and some internal updates.

3. *Could you direct us to published literature on the mechanism of action of 10kHz frequency SCS?*

LM has provided an animal study which the Committee found helpful in understanding the mechanism of action (Cuellar et al, 2012).

4. *LF SCS requires intra-operative paraesthesia mapping to optimise pain relief, which the patient relays through feedback. HF SCS does not require this but instead uses common anatomical landmarks for lead placement. Are the mechanisms of action of LF and HF SCS therefore fundamentally different?*

   Already addressed.

5. *To your knowledge, is the frequency, amplitude (which is variable), and pulse width considered optimal? Is there any on-going research into further optimisation?*

   The current device is the optimal to date, although Nevro are always looking to improve and there is a strong team carrying out ongoing research into how the device can be optimised.

6. *Is the intellectual property of Senza technology protected? Could other companies replicate its success?*

   Nevro hold several international patents relating to the technology.

Population

The population described in the scope is clearly defined, matching the recommendations of TA159 [1] (i.e. management of chronic, severe neuropathic pain in patients recalcitrant to medical management). In this context:

7. *In your experience, what is the main underlying cause of the neuropathic pain in these patients? Is it reflected by the characteristics of patients in the Senza-RCT [2] (i.e. is this trial representative of the patients the NHS should use Senza in)?*

   KM worked on TA159 in 2006/7 (working for a different company). The TA was informed by two RCTs, the PROCESS trial [4]– comparing traditional SCS and Conventional Medical Management (CMM) with CMM only and the trial by North et al. (2015) [3], which investigated the use of LF SCS versus repeated surgery in failed back surgery syndrome. Failed back surgery syndrome (FBSS) is one cause of chronic neuropathic pain, but whether a patient has had back surgery previously is not paramount to whether SCS is a suitable treatment option. This has more to do with definitions around pain. The patients included in the SENZA-RCT were

very similar in characteristics to those reported in the studies informing TA159.

8. *Could you describe the pathway of a "typical" patient, if there is one? That is, what combination of drugs, surgery, and other treatments might have been tried before Senza is considered?*

   The population appear to be a heterogenous group – is there a 'typical' patient? Surgery might be part of the workup. From the literature, c. 85% of SCS patients have failed back surgery syndrome. However, it is not necessary for patients to have had previous back surgery to benefit. Some will have had CMM only. The spread of 85% with FBSS and 15% without surgery is most common in the UK also.

9. *Is the population exactly the same as those who could be treated with LF SCS? Or are there likely to be some patients that benefit more from either technology?*

   See 7 and 10.

10. *Would you consider Senza as a direct replacement for LF SCS or as an alternative? Would introduction of Senza displace existing technology*?

    Nevro would consider Senza SCS as superior to LF SCS, i.e., a replacement. However, it is thought that the technologies have different mechanisms of action, therefore patients that do not respond to one might benefit from the other.

Clinical research

The evidence from TA159 for the use of LF SCS in the treatment of neuropathic pain is derived from two RCTs, the trial by North et al. (2015) [3], which investigated the use of LF SCS versus repeated surgery in failed back surgery syndrome (FBSS) patients, and the PROCESS trial [4], which investigated the use of LF SCS versus continued medical management.

11. *These studies used different LF SCS devices compared with the comparator used in the Senza-RCT trial (which used the Precision Plus System [Boston Scientific]). Are you confident that LF SCS technologies perform equivalently and therefore that the results from the Senza-RCT are generalisable against all available traditional SCS systems?*

    Yes, studies have shown remarkable consistency of LF SCS systems both in terms of responder rates and pain relief, although there has never

been a comprehensive comparison done, and it is unlikely this would be useful. LF SCS systems use similar frequencies are technically equivalent. Most LF SCS systems do not have RCT evidence.

12. *Both these studies were exclusive to patients with FBSS, whereas Senza-RCT recruited a mixed cohort with predominant FBSS. Are you confident these populations are generalisable with each other?*

    Yes. See response to question 8.

13. *The protocol for the Senza-RCT in clinicaltrials.gov (NCT01609972) reported that anticipated recruitment for the trial was 356. However, only 198 patients were recruited for the trial. Is there any reason for this discrepancy?*

    The discrepancy was due to the expected attrition due to eligibility criteria (that is, the sample size included patients who would be expected to be excluded following eligibility screening).

14. *There are a large number of single-armed studies published as abstracts. Are there any plans to synthesise this data as a meta-analysis?*

    No plans within the timelines of this assessment report, but it is a good idea.

15. *Are there any plans for further comparative studies, preferably RCTs, to increase the confidence of the effect and safety of treatment compared with another device or continued medical management?*

    Yes. One (UK based, Guy's hospital) looking at Senza SCS for refractory back pain in patients who have not previously had back surgery. Patients randomised to CMM or CMM plus HF10. They had subgroups like this in the Senza-RCT. Plan is to conduct this trial at Guy's with Al-Kaisy.

16. *Another application of SCS is burst stimulation (St Jude Medical). Are there any plans for comparative trials of Senza HF SCS versus Burst stimulation?*

    [redacted]

[redacted]

Studies with Sham as a comparator

17. *Perruchoud et al. (2013) [5] reported a small cross-over RCT where a HF (5 KHz) Medtronic device was compared with sham treatment. The results of this study were negative, with the authors concluding "It appears that the effect of HFSCS and sham is equal and only the order in the sequence, not the nature of the treatment, seems to dictate the effect". Do you have any opinion on the reasons for the negative results of this study? Is it device or frequency specific?*

[redacted]

[redacted] 'High frequency' is not strictly defined, but several Mechanism of Action type studies and clinical trials suggest the clinical benefit effect begins somewhere around 3 to 4 kHz up to 10kHz maximum, with frequency-dependent results.

18. *In 2011, Nevro sponsored a cross over RCT that was to compare Senza with sham (the device turned off). This has been registered as a protocol see www.isrctn.com/ISRCTN33292457) [6]. This trial was due for completion on 13th December 2012 and no reasons have been given for abandonment. Could Nevro tell us what happened with this study and any data generated from it?*

    Difficulties arose with blinding that challenged the scientific integrity of the trial. For example, the device would normally need 30 to 45 minutes of battery recharge per day. In the sham group, with the device set to zero frequency, it won't lose charge (so subject blinding became ineffective). The trial was therefore discontinued.

Costs and model

19. *We are aware that there has been a cost-utility study already published concerning the cost effectiveness of Senza [7]. This was developed using the structure of economic model used in TA159. For the de novo economic submission, is Nevro planning to use a model similar to or based on this, or is an entirely new de novo model going to be used?*

    KM – economic model will be based on the existing study. A lot of work has already been done on this, and for consistency and ease it makes

sense to build on this. The company have taken sub-groups out of the scope – IW asked if the intention for doing this was to simplify the economic model (1 scenario only consistent with TA159 population). KM – lots of scenarios will be analysed to answer the questions posed. Sub groups were removed, as there were challenges trying to fit patients into the sub groups given, and the model will not get into that level of granularity. The intention is to mirror the model NICE reviewed and accepted in 2007/08. The patient group is essentially the same, so a new approach is not warranted.

20. *We have noted that the Senza device is listed in the NHS supply chain. Will this be the basis of the device cost used in the model?*

    The issue Nevro have is that they don't see comparator costs on Supply Chain due to confidential tender process.

4) Questions for EAC from Nevro

DC had concerns over to what extent the mechanism of action would feature in the report. Low frequency SCS has been an accepted therapy option for 40 years, and the mechanism of action is still not completely understood. Similarly with high frequency SCS, there will be some similarities and some differences. Nevro's priority is to provide clinical evidence that the technology works while research goes on as to how it works. IW and BD reassured him that it is the clinical evidence that is of interest for the report.

5) Next Steps

- Both NICE and the EAC had difficulty in printing the clinical submission – some pages seemed to be set to a non-standard paper size. The fix locally may mean that different page numbers are created, which would be a problem for referring to these in the various assessment reports. Could Nevro please check and resolve this when whole submission (including economic) is made? Nevro agreed to make the final submission in pdf format. This is likely to be sent to NICE on Friday 30th June, i.e. earlier than economic submission is due, since the USA office closes for 4th July holiday.
- EAC's notes from the call will be shared with Nevro for their review and correction of any inaccuracies or omissions.

<u>References</u>

8. National Institute for Health and Care Excellence. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (TA159). Available at www.nice.org.uk/guidance/ta159. London; 2008.
9. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, et al. 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. 2015 Oct;123(4):851-60.
10. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery. 2005;56(1):98-106; discussion -7.
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12. Perruchoud C, Eldabe S, Batterham AM, Madzinga G, Brookes M, Durrer A, et al. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. Neuromodulation. 2013 Jul-Aug;16(4):363-9; discussion 9.
13. Senza™ spinal cord stimulation system for the treatment of chronic back and leg pain in failed back surgery syndrome (FBSS) patients.
14. Annemans L, Van Buyten JP, Smith T, Al-Kaisy A. Cost effectiveness of a novel 10 kHz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS). Journal of long-term effects of medical implants. 2014;24(2-3):173-83.

Appendix 5

Further EAC questions for Nevro from Senza evidence submission.

SENZA RCT

1. In your economic submission, patients enter the Markov model with or without "non-serious complications". The company defined these as adverse events not resulting in device explantation and included events "such as lead migration, device dislocation, implant site pain, surgical site infection, delayed wound healing and paraesthesia". The proportion of these adverse events were calculated from an individual-patient analysis of the SENZA-RCT data that was not made available to the EAC (your ref. 31 in the submission), so cannot be independently verified. The company estimated that [redacted] Please provide the EAC with the individual patient level data that were used to calculate these events.

2. The company has quoted an [redacted] for Senza HF10 therapy in the submission, but we see a list price for the IPG(alone) in NHS Supply Chain catalogue of [redacted]. NHS Supply Chain also has additional pricing available for various accessories / consumables required for the SCS procedure. Can you please provide a detailed breakdown of the [redacted] into its constituent items and cost of each?

3. Furthermore, in the submission, you state that:

   "In a separate analysis the commercial in confidence NHS Supply Chain catalogue price for HF10™ therapy [redacted] is used as an alternative to the published and subsequently inflated HF10™ therapy cost (£16,648). It should be noted that a publicly available NHS Supply Chain price is not available for TNR-SCS and TR-SCS, therefore the inflated costs from Taylor et al. (2010) are used in this analysis for these devices. It should also be noted that any hospital can order direct from the NHS Supply Chain catalogue at the price stated above [redacted]) for HF10™ therapy, irrespective of volume ordered and in the absence of a contractual commitment to any volume."

   By inferring a direct comparison between the £16,648 (Taylor, 2010 inflated) and an NHS Supply Chain price of [redacted], you suggest that

neither of these figures includes any procedural costs (such as consultation, investigations, surgery and hospital admissions). We would not normally expect the NHS Supply Chain price to include anything but device and accessories / consumables as per the acquisition of the system. Please therefore also provide the breakdown of the £16,648 into its constituent items and costs.

4. The SENZA-RCT was reported as conducted in 10 centres in Kapural 2015 and 11 centres in Kapural 2016. Which is correct please & why the difference?

5. Seeking further understanding of the patient numbers reported in Kapural 2015 and Kapural 2016 please:

   Can you explain the 'randomised cohort' in Baseline Demographics and Clinical Characteristics (Table 1 of both papers)? These are reported for n=92 in HF-10 group and n=87 in Traditional SCS group.

   Where do these patient numbers fit in the Study subject flow charts of Figure 1 in both papers?

6. The one patient in each arm removed from Kapural 2016 at 12 months (see flow chart in Figure 1) seemingly were reported at 12 months in Kapural 2015. Is there an explanation for this discrepancy?

Appendix 6

Further EAC questions for Nevro from Senza evidence submission.

SENZA RCT

1. In your economic submission, patients enter the Markov model with or without "non-serious complications". The company defined these as adverse events not resulting in device explantation and included events "such as lead migration, device dislocation, implant site pain, surgical site infection, delayed wound healing and paraesthesia". The proportion of these adverse events were calculated from an individual-patient analysis of the SENZA-RCT data that was not made available to the EAC (your ref. 31 in the submission), so cannot be independently verified [redacted]. Please provide the EAC with the individual patient level data that were used to calculate these events.

   This table will be sent separately.

2. The company has quoted an NHS Supply Chain list price of [redacted] for Senza HF10 therapy in the submission, but we see a list price for the IPG(alone) in NHS Supply Chain catalogue of [redacted] NHS Supply Chain also has additional pricing available for various accessories / consumables required for the SCS procedure. Can you please provide a detailed breakdown of the [redacted] into its constituent items and cost of each?

   [redacted]

3. Furthermore, in the submission, you state that:
   "In a separate analysis the commercial in confidence NHS Supply Chain catalogue price for HF10™ therapy [redacted] is used as an alternative to the published and subsequently inflated HF10™ therapy cost (£16,648). It should be noted that a publicly available NHS Supply Chain price is not available for TNR-SCS and TR-SCS,

therefore the inflated costs from Taylor et al. (2010) are used in this analysis for these devices. It should also be noted that any hospital can order direct from the NHS Supply Chain catalogue at the price stated above [redacted] *for HF10™ therapy, irrespective of volume ordered and in the absence of a contractual commitment to any volume."*

By inferring a direct comparison between the £16,648 (Taylor, 2010 inflated) and an NHS Supply Chain price of [redacted], you suggest that neither of these figures includes any procedural costs (such as consultation, investigations, surgery and hospital admissions). We would not normally expect the NHS Supply Chain price to include anything but device and accessories / consumables as per the acquisition of the system. Please therefore also provide the breakdown of the £16,648 into its constituent items and costs.

The comparator device costs are taken from Taylor et al 2010. As a peer-reviewd publication which states on page 465:

"In 2008 prices provided by Medtronic, Inc, a non- rechargeable IPG costs £7761 (Synergy, Medtronic, Inc, Minneapolis, MN) and its replacement costs £7177. The nonrechargeable IPG system cost £9762 and a replacement system cost £9085 (Table 2). The rechargeable IPG system (Restore Ultra, Medtronic, Inc, Minneapolis, MN) cost £15,076 and a replacement system cost £12,860."

These costs are not further broken down beyond IPG and whole system stated above.

4. The SENZA-RCT was reported as conducted in 10 centres in Kapural 2015 and 11 centres in Kapural 2016. Which is correct please & why the difference?

   A total of 11 centres enrolled subjects, but one centre enrolled only one subject who upon evaluation did not meet eligibility criteria and therefore was not randomized. A total of 10 centers randomized subjects.

5. Seeking further understanding of the patient numbers reported in Kapural 2015 and Kapural 2016 please:

   Can you explain the 'randomised cohort' in Baseline Demographics and Clinical Characteristics (Table 1 of both papers)? These are reported for n=92 in HF-10 group and n=87 in Traditional SCS group.

   Where do these patient numbers fit in the Study subject flow charts of Figure 1 in both papers?

   Table 1 in both publications presents baseline characteristics for the per protocol (PP) population, which is defined in the Methods section of Kapural 2016 as subjects who completed a primary endpoint assessment. Of the 101 subjects randomized to HF10 therapy, 9 were excluded from the PP analysis leaving 92 subjects as reported. Of the 97 subjects randomized to HF10 therapy [SIC], 10 were excluded from the PP analysis leaving 87 subjects as reported.

6. The one patient in each arm removed from Kapural 2016 at 12 months (see flow chart in Figure 1) seemingly were reported at 12 months in Kapural 2015. Is there an explanation for this discrepancy?
   As reported in Figure 1 of Kapural 2016, one subject was incarcerated and one subject was lost to follow-up after IPG implant but prior to the 12 month follow-up. These subjects were included in intention-to-treat analyses (as treatment failures) but excluded from per protocol analyses. Figure 1 of Kapural 2015 did account for these subjects.

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Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

Senza Spinal Cord Stimulation (SCS) System for the treatment of chronic pain

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Newcastle upon Tyne Hospitals (NUTH) and York Health Economics Consortium (YHEC) External Assessment Centre (EAC) to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **07 August 2007** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

02 August 2017

NICE National Institute for Health and Care Excellence

Issue 1 Page 168 Appendix E & Page 70, Table 4.3 on Page 71 (and any other occurrences)

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Missing markings for Commercial in Confidence in the EAC report	NHS Supply Chain contractual price of a Senza system and of a Senza IPG price should be marked as Commercial in Confidence throughout the document. (Commercial in Confidence)	Incorrectly labelled as not CIC	Thank you. We have edited the text to reflect your comments.

Issue 2 Page 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"More recently, at least two new SCS technologies have been developed that do not induce paraesthesia in patients. These are the Burst SCS system (St Jude Medical) and the high frequency Senza system (De Ridder et al., 2015);"	Request to remove the statement which incorrectly claims that Burst Stimulation does not induce paraesthesia.	It is unclear why has Burst stimulation has been characterised as "not inducing paraesthesia in patients". This is not strictly correct. Burst SCS System is not labelled as paraesthesia-free and requires paraesthesia mapping for placement. The recent pivotal RCT "SUNBURST" demonstrated reduced paraesthesias among the cohort but at least 35% continuing paraesthesia.	Thank you. We have left BURST in because it is of background interest. We edited the wording to say BURST reduces paraesthesia rather than eliminates it.

Issue 3 Page 12 - Footnote to table 2.1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"HF10 SCS waveform consists of a biphasic charge-balanced pulse train with pulse widths usually set to 30 µsec and a pulse rate of 10 kHz. Low frequency SCS produces a tonic waveform in which pulses are delivered at a consistent frequency, pulse width, and amplitude."	Request description of HF10SCS is changed to explain that frequency and pulse width are fixed with HF10.	Incorrect. Both HF10 and low frequency SCS use a tonic waveform however frequency and pulse width are fixed with HF10 but widely variable with low frequency SCS.	We have assumed this means that [concerning traditional SCS] these parameters are variable between devices and have edited the text to reflect this. We have removed reference to the word "tonic".

Issue 4 Page 16 and page 17 table 2.3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The estimate of clinical effectiveness of traditional low frequency SCS was derived from two randomised controlled trials (RCTs). The PROCESS trial (Prospective Randomised Controlled Multicentre Trial of the Effectiveness of Spinal Cord Stimulation) enrolled 100 patients with neuropathic back and leg pain who had failed back surgery syndrome	Request correction of the characterisation of predominant back pain patients in the description of the North and Kumar papers.	Both North and Kumar (PROCESS) trials patients needed to have predominant leg pain to be included into both studies. Kumar et al reported both leg and back pain whilst North et al reported only leg pain.	Thank you. We have edited the text to reflect your comments.

(FBSS), and compared the use of low frequency SCS with conventional medical management (CMM) (Kumar et al., 2007)." *"The trial by North et al. (2005) was designed to compare the efficacy of low frequency SCS with reoperation in patients with FBSS (North et al., 2005)."*			

Issue 5 Page 17 – Table 2.3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Senza RCT "241 selected as eligible for treatment"	Request correction of this sentence to read "241 subjects assessed for eligibility"	Current statement is not correct.	Thank you. We have changed this.

Issue 6 Page 27 – Table 3.1 – EAC Comments

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Loss to follow up substantial using ITT analysis."	Request correction of EAC characterisation of "substantial"	We don't believe the loss to follow up was 'substantive'. as 20% which would be generally regarded as the cut off for acceptable loss. In addition, trial analyses conducted showed that	We have calculated the loss to follow up after 24 months as 16% in the Senza arm and 27% in the low frequency SCS arm. Although there are no objective measures of when loss to follow up causes significant

		when the results for patients with loss to follow up were imputed that there was no impact of the ITT finding.	potential for bias, statisticians have reported a 5% loss as not important, whereas a 20% loss is likely to have the potential to significantly affect results [1]. The overall attrition rate was around the 20% level so we think the use of the adjective "substantial" is justified. We have adjusted the text to clarify this.
1. Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child. 2008 Jun;93(6):458-61.			

Issue 7 Page 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Loss to follow up substantial using ITT analysis."	Request correction of EAC characterisation of "substantial"	We don't believe the loss to follow up was 'substantive'. as 20% which would be generally regarded as the cut off for acceptable loss. In addition, trial analyses conducted showed that when the results for patients with loss to follow up were imputed that there was no impact of the ITT finding.	Our calculations show that overall the loss to follow up was 21% across both arms after 24 months. Results of imputation were not reported in the published papers. We have adjusted the text to clarify this.

Issue 8 Page 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"uneven at 24 months, the EAC considered the risk of attrition bias was relatively high."	Request definition or description of "relatively high"	We don't believe the loss to follow up was 'substantive'. as 20% which would be generally regarded as the cut off for acceptable loss. In addition, trial analyses conducted showed that when the results for patients with loss to follow up were imputed that there was no impact of the ITT finding.	From Figure 1 of Kapural et al. (2016), attrition at 24 months is: 85/101 for Senza. 71/97 for low frequency SCS. Although not quite statistically significant, loss to follow up appears likely to be uneven. *No action*.

Issue 9 Page 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Nevertheless, the reporting was not considered to be fully transparent, and there were particular issues with the lack or reporting of devices that had been explanted"	Cross-reference that these data have been provided separately by Nevro as Commercial in Confidence as they have elsewhere in the report.	Whilst we accept the SENZA trial publications did not fully detail the explant differential, Nevro have provided these data to the EAC as part of the process. The EAC make reference to the data provided by Nevro elsewhere in the report. (specifically Pages 45 and 67).	The EAC is primarily responsible for critiquing the *published* evidence, which has been peer-reviewed and otherwise met the criteria for suitability for publication. Whilst we appreciate we have received the explantation data as commercial in confidence, this has not been transparently reported in public so remains a valid criticism.

			No action.

Issue 10 Page 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Longitudinal VAS data was aggregated using mean results with standard error of mean (SEM) represented graphically. In the opinion of the EAC, this did not transparently report the inter- and intra-patient variability of responses over time."	Request change to include acknowledgement that the analysis was done but not reported in the publication in full detail.	Whilst we agree with EAC's comments, we would note that the repeated measures data was analysis undertaken in the SENZA RCT does take account of the differences between groups over time and is therefore not a source of 'high risk of bias. However for purposes of simplification in the publication the plot only shows standard error.	Whilst the EAC understands the need for brevity in published papers, we feel that more description on the variability of patient responses would have been enlightening. We have replaced the word "transparently" with "fully" so as not to suggest data was deliberately withheld or misleading.

Issue 11 Page 38

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"In section 7.6.2 of the submission, the company states that no analyses other than intention-to-treat (ITT) were conducted and included in their Table 22 summary of outcomes from the SENZA-	None. This was an inadvertent error in the description of the analyses conducted. The EAC has correctly described the analyses undertaken. We thank the EAC for pointing out this correction.	N/A	Thank you.

RCT. This is factually incorrect, as the published papers (Kapural et al. 2015 and Kapural et al. 2017) describe three cohorts for the analyses: ITT, per protocol (PP) and those receiving a permanent SCS implant (PI)."			

Issue 12 Page 41

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"However, there was some suggestion from the longitudinal graphs that the therapeutic effect diminished with time (Figure 10 of company's submission). It is not possible to confidently extrapolate data beyond the 24 months reported. Therefore, the EAC concludes that the clinical evidence suggests that pain relief is achieved for a minimum of 24 months."	Request removal of the statement referring to a "diminishing treatment effect over time".	Figure 10 does not show a diminishing treatment effect over time.	From figure 10. Back pain, leg pain (VAS, cm): 6 months: 2.7, 1.4 12 months: 2.8, 2.0 24 months 3.3, 2.3 Thus compared with 6 months, the effect at 24 months was diminished by 18% for back pain and 39% for leg pain. The EAC accepts this data is inconclusive but *may* indicate a trend for diminishing effect. We have adjusted the wording but otherwise retained this statement.

Issue 13 Page 55

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"However, when the EAC repeated this search, it was found that the company had potentially confused UK and US date formats in entering the search into the MAUDE database. This had the effect of searching only the month of December 2016 in identifying the 15 records described by the company in their submission. Correcting this date format error, the EAC found that there were 131 records in the whole of 2016."	None. We acknowledge the inadvertent error in data extraction and thank the EAC for correcting this.	N/A	Thank you.

Issue 14 Page 57

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The authors reported there was a highly significant "period" effect regarding the time of treatment, but that high frequency SCS was not	Request correction of the statement to read "5kHz high frequency stimulation"	It is not possible to characterise all High Frequency stimulation using a single statement.	Added "at 5 Hz" to clarify text further.

statistically significantly superior to placebo"			

Issue 15 Page 59

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The study reported results from a health economic model of SCS which had a UK NHS perspective, a 15 year life and compared HF10 therapy with CMM, reoperation, and traditional rechargeable and non-rechargeable low frequency SCS technology.	We suggest change "15 year life" to "15 year time horizon"	Ambiguous whether the comment refers to the battery longevity or the time horizon of the model.	Thank you. We have changed this accordingly.

Issue 16 Page 64

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The EAC considers that the handling of complications is not transparent in the model structure"	Request the EAC qualify this with a statement cross-referencing the reason for this. Those reasons are simplification and clarification that the model structure presented follows closely the previously published and accepted Spinal Cord Stimulation economic model developed by ScHARR. NICE have already considered that model as part of TA159 evaluation.	The model diagram is intended as a simplification of the model structure and is reflective of that presented in previous economic evaluations including the model developed by the School of Health and Related Research (ScHARR) for NICE TAG159. {Simpson EL, et al. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin:	Thank you for the clarification. We have re-written the text in this section to reflect your comments

		systematic review and economic evaluation. Health Technol Assess. 2009;13(17):iii, ix-x, 1-154.} All of the complications that occur in the decision tree are assumed to be short-term and the analysis conservatively assumes that the complications do not result in movement between the optimal and sub-optimal. Since these events are short term and are assumed not to influence the pain relief state and therefore patients simply enter the Markov model in either optimal or sub-optimal pain (i.e. they do not persist in the Markov phase of the analysis). While an extended model structure could be presented graphically, because we don't know the proportion of patients whose complications persist, those that are resolved and those that are new in each cycle, this approach would be difficult to implement practically. Instead,	

		within the Markov engine a proportion of patients in the optimal and sub-optimal states are assumed to experience an AE each cycle (independent of their previous states), at the rate specified, and these patients are considered separately, with regards to utilities and costs. Incorporating separate health states to differentiate those patients with and without complications would infer a difference in movement between health states. Our current approach assumes that complications do not influence pain relief and, given HF10 has a lower rate of complications, can therefore be considered conservative. Whilst we accept that it may have technically possible to make the model more complex by introducing separate states for complications, we contend that there is no reason for this increased complexity and the results of the model would not alter. We therefore argue for the	

		parsimony in our model structure.	

Issue 17 Page 69

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Material source of uncertainty of cost uncertainty"	A statement clarifying the importance or otherwise of this cost uncertainty.	Whilst there is some uncertainty this does not make a difference to the outcome according to the sensitivity analysis results. In addition we have included analysis using national NHS tariff which reflects actual costs to commissioners. Both these methods support the general direction of the results presented.	The EAC considers that the lack of granularity within bundled costs does represent a source of uncertainty, so this is not factually incorrect. We report the results of the sensitivity analysis elsewhere. *No change*.

Issue 18 Page 81 – Figure 4.5 (A) & (B)

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Unclear from figure title whether they include or exclude procedural aspects	Request clarification whether these costs presented in the charts include procedural elements or devices only.	Clarity of interpretation	These graphs were taken directly from the company submission and implicitly *include all costs*. As discussed elsewhere in the document, procedural costs were not included in the base case analysis, as it was assumed procedural costs were equivalent and would cancel

			each other out for each technology. However, there were errors in the legend which have been rectified

Issue 19 Page 161 – Table D4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Source of assumption was originally from economic evaluation by the Association of British Healthcare Industries (ABHI) (Simpson et al., 2008). Range of 2 to 10 years used in TA 159 model. Substantial uncertainty.	Request correction of the source of the 4 year battery life expectancy for non-rechargeable SCS systems was from observational data published in Kumar et al. 2006.	Incorrect source referenced	We have corrected this citation.

Issue 20 Page 166 – Table D4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Unpublished data could not be corroborated by EAC."	Request change of wording to align with page 67 where this is explained that "These data were made available to the EAC and have been independently verified."	Inconsistent description	Thank you. We have corrected this mistake.

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Issue 21 Page 166 – Table D4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Longer-term non serious adverse effect parameters could not be verified by EAC"	Request change of wording to align with page 67 where this is explained that "These data were made available to the EAC and have been independently verified."	Inconsistent description	Thank you. We have corrected this mistake.

NICE National Institute for Health and Care Excellence

Medical Technologies Evaluation Programme

MT330 – Senza Spinal Cord Stimulation (SCS) System for chronic pain

Specialist commentator questionnaire responses

Name of Specialist Commentator	Job title	Organisation
Dr Sarah Love-Jones	Pain Consultant	North Bristol NHS Trust
Ms Karen Sanderson	Advanced Nurse Practitioner	Guy's and St Thomas' NHS Trust
Dr Tim Johnson	Consultant in Pain Management	Salford Royal NHS Foundation Trust
Mr Girish Vajramani	Consultant Neurosurgeon	University Hospital Southampton NHS Foundation Trust
Dr Ganesan Baranidharan	Consultant in Pain Medicine & Anaesthesia	Leeds Teaching Hospital NHS Foundation Trust

Comments on specific sections of the draft Topic Briefing

Dr Sarah Love-Jones **Pain Consultant**	**Page 4, Paragraph 3**	**Senza HF10 therapy should be added to low frequency paraesthesia-based SCS, not replace it. There are still some patients who prefer paraesthesia SCS**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Page 4, Paragraph 3**	**This technology provides high and low frequency For certain conditions low frequency is the first option There is not current robust evidence that for all neuropathic pain for low frequency is not effective**
Dr Tim Johnson **Consultant in Pain Management**	**Page/section**	**Blank**
Mr Girish Vajramani **Consultant Neurosurgeon**	**1. Page 2** **2. Pages 10,11,12** **3. Page 11**	**Intra-operative CT imaging is used to confirm accurate placement/positioning of the electrodes and leads** **should be replaced by** **Intra-operative image intensifier is used .....** **Nevero** **Should be replaced by** **Nevro** **this applies to all sections where Nevro has been misspealt as Nevero** **HF10™ spinal cord stimulation in the treatment of refractory chronic migraine: ISRCTN registry identifier: ISRCTN94247798. Status: ongoing. Indication: chronic migraine that has not responded to established therapies. Devices: Senza SCS System, Nevero.** **This has been duplicated.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**		**Comments provided in separate document**

Your opinion on how this technology would be used in practice

Question 1: How do you rate this technology's level of innovation? Is it a minor variation on existing technologies or does it represent a novel concept/design?

Dr Sarah Love-Jones **Pain Consultant**	**This is a major innovation, the device structure is similar to other spinal cord stimulator devices, it is the therapy and the frequency of the stimulation which represents a novel concept and appears to superior in treating failed back surgery syndrome**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**This technology has been innovative in opening up the field of spinal cord stimulation for 35 years we used low frequency stimulation which had limitations especially with patients with predominate back pain. Senza was the first implant to allow parathesia free stimulation and now pain neuromodulation specialist are researching different types of frequencies all parathesia free.Response**
Dr Tim Johnson **Consultant in Pain Management**	**It could represent a major development in pain management. Currently, despite demonstrated benefit in an open study against conventional stimulation, there are no good studies that assess the effect of HF stimulation at 10K Hz against placebo, which is a problem because there is a good study using HF 5KHz that demonstrates no benefit. My belief is that further clinical investigation is required before the technology is rolled out widely.**
Mr Girish Vajramani **Consultant Neurosurgeon**	**It is a Novel concept and a major variation on the existing traditional SCS technology.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**This was a huge shift to our understanding on waveforms in spinal column stimulation. They also changed the evidence base and has made rest of the companies invest into to research and innovation.**

Question 2: Would users of this technology require any special training?

Dr Sarah Love-Jones **Pain Consultant**	**No further special training to that needed for conventional spinal cord stimulation**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Yes initially with the programming of this device although is less time consuming as there is no mapping of parathesia over the painful area therefore you do not need to ensure patients are comfortable with the parathesia. Lead placement in theatres is the same procedure as currently**
Dr Tim Johnson **Consultant in Pain Management**	**Not beyond the training required for conventional SCS.**

Mr Girish Vajramani **Consultant Neurosurgeon**	**No**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**This is much easier than the previous technologies and no special training is needed**

Your experience with this technology

Question 3: Are you familiar with the technology?

Dr Sarah Love-Jones **Pain Consultant**	**Yes. I have been using this device for chronic pain patients with back and leg pain since 2011**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Yes**
Dr Tim Johnson **Consultant in Pain Management**	**Yes I am**
Dr Girish Vajramani **Consultant Neurosurgeon**	**Yes**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**yes**

Question 4: Have you used this technology before? Do you use it currently?

Dr Sarah Love-Jones **Pain Consultant**	**Yes, I currently use this HF10 spinal cord stimulation technology for patients suffering with chronic low back and leg pain with similar results to the PROCESS study(Kapural et al 2016)**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Currently using this technology along with all of the other named stimulators**

Dr Tim Johnson **Consultant in Pain Management**	**I work very closely with colleagues who implant both conventional and high frequency spinal cord stimulation devices. I am involved in the assessment of patients referred for the procedure but I do not implant or manage these devices myself.**
Dr Girish Vajramani **Consultant Neurosurgeon**	**Yes and I currently use this technology**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**I have used this for a long time now and we have more than 150 patient implanted with very good outcomes**

Question 5: If so how regularly and how many times?

Dr Sarah Love-Jones **Pain Consultant**	**I have implanted 63 patients with NEVRO HF10 Senza spinal cord stimulator devices**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Since 2010 as part of a research trial and clinically daily with follow up patients**
Dr Tim Johnson **Consultant in Pain Management**	**See above**
Dr Girish Vajramani **Consultant Neurosurgeon**	**About 60-80 implants a year**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	***We perform at the least 6-8 cases per month***

Question 6: Were you involved in the development/testing of this technology?

Dr Sarah Love-Jones **Pain Consultant**	**No. I used the technology after it was CE Marked**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Yes I was part of the European multi centre research Al Kaisy Van Buyten J smet et al 2012**

Dr Tim Johnson **Consultant in Pain Management**	**I was originally involved in the HTA assessment of Spinal Cord Stimulation and have followed developments since then.**
Dr Girish Vajramani **Consultant Neurosurgeon**	**No**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**No**

Question 7: Has this technology been superseded or replaced already?

Dr Sarah Love-Jones **Pain Consultant**	**No, it is still current**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**No, although there are other types of frequencies being researched**
Dr Tim Johnson **Consultant in Pain Management**	**Not that I am aware of - there appear to be a host of stimulator type pain technologies being brought onto the market.**
Dr Girish Vajramani **Consultant Neurosurgeon**	**No**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**This has enabled us to treat the low back pain. This was not easy with the past therapies. Hence our patient numbers who benefit from neuromodulation has increased significantly**

Patient impact

Question 8: How could this technology improve patient health outcomes? Are there any groups of people who would particularly benefit?

Dr Sarah Love-Jones **Pain Consultant**	**This therapy benefits patients with Failed back surgery syndrome and is superior in treating low back pain after all other treatments have failed. Patients who benefit particularly are those who cannot tolerate the paraesthesia (tingling sensation) in conventional spinal cord stimulation (SCS). The Senza HF10 therapy is paraesthesia free. Patients are able to drive with the Senza sytem.**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Predominately neuropathic back pain where low frequency has been difficult to capture. Patients have often been offered back surgery and there pain and disability has not improved.**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani **Consultant Neurosurgeon**	**It has a made a major difference to the patient health. Traditional SCS technology failed to provide meaningful reduction in low back pain, where as the high-frequency system has provided significant reduction in back pain. Patients with FBSS with low back pain with or without neuropathic leg pain would benefit most**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**Currently strong evidence is available for failed back surgery syndrome. There are ongoing trials in neck pain, vascular, CRPS and various other neuropathic pain conditions. Anyone with refractory neuropathic pain would benefit from this therapy. Treatment algorhythms for all these conditions will be available soon**

Question 9: How could it change patient experience? Would it lead to fewer hospital visits, less invasive treatment or other benefits for patients?

Dr Sarah Love-Jones **Pain Consultant**	**This treatment changes the patient experience in that they do not experience the paraesthesia of other SCS devices and do not get postural changes in the therapy. The lead positioning in the operating theatre is quicker as no on-table patient testing is required, therefore allowing more patients be operated on in any one session**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Patients prefer being parathesia free this allows them to move freely without having to change the amplitude as with low frequency the parathesia often increases with positioning. Patients require less reprogramming visits to a specialist unit.**

Dr Tim Johnson **Consultant in Pain Management**	Blank
Dr Girish Vajramani **Consultant Neurosurgeon**	**Previously patients with back pain or back and leg pain were denied SCS as the traditional SCS would not work on back pain. With the advent of high frequency system, the practice has changed significantly . Patients are undoubtedly derived enormous benefits with this technology. As the therapy is paraesthesia independent, patients do not get any added sensations. There is no need to do paraesthesia mapping as the placement of the electrode is anatomical. This reduces the surgical time in theatre.** **This would certainly lead to fewer hospital visits with concomitant reduction in analgesic medications.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**With a significant reduction in pain, we find people increasing their activities including return back to work and enjoy their social life more.**

Question 10: Are you aware of any safety alerts for this technology?

Dr Sarah Love-Jones **Pain Consultant**	No
Ms Karen Sanderson **Advanced Nurse Practitioner**	No
Dr Tim Johnson **Consultant in Pain Management**	Blank
Dr Girish Vajramani **Consultant Neurosurgeon**	No
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	None

System impact

Question 11: How would use of this technology impact on NHS services?

Dr Sarah Love-Jones **Pain Consultant**	**Due to no requirement for on table testing (as in other SCS devices), more patients can be treated with HF10 at any one time, using less operating theatre time**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**The treatment is already with in the nice guidelines and offered at specialist centres.**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani **Consultant Neurosurgeon**	**I would foresee an increase in the number of patients needing this technology, improvement in quality of life, return to work and reduction in analgesic medication.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**We currently use this technology in our unit with very good outcomes. We have a good MDT team, which selects the appropriate patients for this therapy. We still haven't reached the numbers in the NHS as this is effective therapy and on the longer run cost saving as assessed by NICE Tag 0159**

Question 12: Would any changes in facilities or infrastructure be needed for this technology to be used?

Dr Sarah Love-Jones **Pain Consultant**	**No changes in infrastructure needed from conventional SCS**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Existing centres who provide spinal cord stimulation would be able to adopt this technology with in their existing facilities**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani **Consultant Neurosurgeon**	**No**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**None specific as long as they perform neuromodulation already**

Question 13: Do you think that use of this technology could lead to cost savings for the NHS?

Dr Sarah Love-Jones **Pain Consultant**	**Compared to conventional medical management this therapy is cost effective for Failed back surgery syndrome.**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**There is a reduction in procedure time, programming time and less follow up appointments.**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani **Consultant Neurosurgeon**	**Yes**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**Yes as per NICE tag 0159**

Any other comments or opinions on this technology (optional)

Dr Sarah Love-Jones **Pain Consultant**	**None**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**This technology being parathesia free allows for improved research in exploring double blinded randomised control trials to evidence further the effectiveness of this treatment. Our centre has applied for a research grant (not industry funded) for patients who have predominately back pain prior to spinal surgery. An efficacy study of 20 patients has highlighted a larger multicentre trial is needed.** **Neuromodulation. 2017 Jan;20(1):63-70. doi: 10.1111/ner.12563. Epub 2016 Dec 26.** **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.** **Al-Kaisy A1, Palmisani S1, Smith TE1, Pang D1, Lam K2, Burgoyne W3, Houghton R4, Hudson E5, Lucas J2**

Dr Tim Johnson **Consultant in Pain Management**	**I need to point out that I am by nature cautious about the claims of new pain technologies. These views are my own (although I do represent the British Pain Society on matters to do with NICE)**
Dr Girish Vajramani **Consultant Neurosurgeon**	**Blank**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**Blank**

Answers to additional questions:

Question 14: What would you deem as standard care for patients with chronic pain of 6 months or more of the trunk or limbs in patients who have failed conventional medical management?

Dr Sarah Love-Jones **Pain Consultant**	**Spinal Cord Stimulation (SCS) is standard care for patients with Failed Back Surgery Syndrome (FBSS) and Complex Regional Pain Syndrome (CRPS) [not all patients with chronic pain] once they have tried conventional medical management and conventional pain clinic treatments for 6 months.**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Physiotherapy /Psychology /Medication management (ie Anti neuropathic medication or opioid management often reducing)/Injection therapy ie epidural /medial branch blocks /facet denervation.** **All of the above treatments would work together rather than individual treatments. If no response to the above treatments refer to a Pain management programme depending on the patients condition either prior to a trial or post a trial of spinal cord stimulation.**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani	**The standard care here would be to consider Spinal Cord Stimulator.**

Consultant Neurosurgeon	
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**we currently use SCS if they have neuropathic pain**

Question 15: What is conventional medical management?

Dr Sarah Love-Jones **Pain Consultant**	**Conventional medical management includes medications, injections, TENS, Acupuncture, Physiotherapy and Pain Management.**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Physiotherapy +/- psychology and medication management**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani **Consultant Neurosurgeon**	**This would comprise medical management, psychology based approaches, physiotherapy, interventional techniques etc.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**Drugs, Physio, Psycology interventions, Pain Management program, surgery, injections ect**

Question 16: Are you aware how much your organisation paid for a Senza SCS system?

Dr Sarah Love-Jones **Pain Consultant**	**The Senza system includes 3 x leads (1x trial lead and 2 x permanent leads) and 1 x IPG (battery). This costs North Bristol Trust £1200 per lead and £11,200 per IPG.**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Nevro has a commercial contract with the trust**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani **Consultant Neurosurgeon**	**About £15000-£20000 depending on the components used.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**No. We had a very low price and i can direct you to our supplies as i keep away from finances. This will change from April 2017 as they are supplied from NHS supplies as zero cost to our trust**

Question 17: Are you aware of how much standard care costs per patient?

Dr Sarah Love-Jones **Pain Consultant**	**I don't know the costs of medical management but NICE TAG 159, 2008 states that SCS is cost effective compared to conventional medical management.**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**No I would suggestcontacting a health economist. Rod Taylor has a lot of expertise in spinal cord stimulation research trials and was part of the process study** **Taylor, Rod R.Taylor@exeter.ac.uk**
Dr Tim Johnson **Consultant in Pain Management**	**Blank**
Dr Girish Vajramani **Consultant Neurosurgeon**	**About £20000-£23000.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**Depends on length. This is well documented in the NICE tag 0159**

CONFLICTS OF INTEREST

PERSONAL FINANCIAL INTERESTS

Specialist commentators	Consultancies or directorships	Clinicians receiving payment for a procedure	Fee-paid work	Shareholdings	Financial interest in a company's product	Expenses and hospitality	Funds	Personal non-pecuniary interest
Dr Sarah Love-Jones **Pain Consultant**	**Yes**	No	**Yes**	No	No	No	No	No
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Yes**	No	No	No	No	No	No	No
Dr Tim Johnson **Consultant in Pain Management**	No	No	No	No	No	No	No	No
Dr Girish Vajramani **Consultant Neurosurgeon**	**Yes**	No	No	No	No	No	No	No
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**Yes**	No	No	No	No	No	No	No
Conflict(s) declared								
Dr Sarah Love-Jones **Pain Consultant**	**I am a medical Consultant to Nevro Corporation, Boston Scientific and St Jude Medical (all Spinal cord stimulator device companies)**							
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Honorary Contract with Nevro for educational lectures**							

Dr Girish Vajramani **Consultant Neurosurgeon**	**Has been on the Nevro Clinical Advisory Board involving occasional meetings for which expenses are covered.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**I have a consulting aggrement with various neuromodulation companies and also on their advisory group (St Jude Medical, Nevro Corporation and Boston Scientific. Have a consultancy aggrement and shares from a new start up neuromodulation company (Nalu Medical)**

CONFLICTS OF INTEREST (cont.)

PERSONAL NON-FINANCIAL INTERESTS

Specialist commentators	Expressed a clear opinion reached as a conclusion of a research project or in a published statement	Been an author on a document submitted as an evidence publication to a NICE advisory committee	Hold office in a professional organisation, charity or advocacy group with a direct interest in the topic	Have any other reputational risks in relation to the topic
Dr Sarah Love-Jones **Pain Consultant**	**Yes**	**Yes**	**Yes**	**Yes**
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Yes**	**Yes**	**Yes**	**Yes**
Dr Tim Johnson **Consultant in Pain Management**	No	No	No	No
Dr Girish Vajramani **Consultant Neurosurgeon**	No	No	No	No
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	No	No	**Yes**	No
Conflict(s) declared				
Dr Sarah Love-Jones **Pain Consultant**	**I have presented data at scientific conferences on spinal cord stimulation outcomes on my patients implanted with spinal cord stimulator devices from Nevro, Boston Scientific and St Jude Medical**			

Ms Karen Sanderson **Advanced Nurse Practitioner**	**Current application of research grant awaiting approval.**
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**I am the secretary for the Neuromodulation Society fo UK and Ireland**

CONFLICTS OF INTEREST (cont.)

NON-PERSONAL INTERESTS

Specialist commentators	Grant for the running of a unit	Grant or fellowship for a post or member of staff	Commissioning of research	Contracts with or grants from NICE
Dr Sarah Love-Jones **Pain Consultant**	Blank	Blank	**Yes**	Blank
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Yes**	No	**Yes**	No
Dr Tim Johnson **Consultant in Pain Management**	No	No	No	No
Dr Girish Vajramani **Consultant Neurosurgeon**	**Yes**	**Yes**	No	No
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	No	**Yes**	No	**Yes**
Conflict(s) declared				
Dr Sarah Love-Jones **Pain Consultant**	**My NHS trust receives research funding for clinical trial with Boston Scientific Spinal cord stimulation devices.**			
Ms Karen Sanderson **Advanced Nurse Practitioner**	**Nevro has sponsored research grants within the research department**			
Dr Girish Vajramani **Consultant Neurosurgeon**	**The pain physiotherapy post is part funded by Nevro for two years before being absorbed by the NHS**			
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	**I have received unrestricted educational grant from Nevro Corp and St Jude medical for research.** **I am currently a GDG member of NICE Pancreatitis group**			

LINKS/FUNDING FROM THE TOBACCO INDUSTRY

Specialist commentators	Yes or No?	*Conflict(s) declared*
Dr Sarah Love-Jones **Pain Consultant**	No	None
Ms Karen Sanderson **Advanced Nurse Practitioner**	No	None
Dr Tim Johnson **Consultant in Pain Management**	No	Blank
Dr Girish Vajramani **Consultant Neurosurgeon**	No	Blank
Dr Ganesan Baranidharan **Consultant in Pain Medicine & Anaesthesia**	No	Blank