

Senza Spinal Cord Stimulation (SCS) System for the treatment of chronic pain

Produced by: Newcastle upon Tyne Hospitals (NUTH) and York Health Economics Consortium (YHEC) External Assessment Centre (EAC).

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Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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Abbreviations

Term	Definition
AE	Adverse event
CI	Confidence interval
CMM	Conventional medical management
CRPS	Complex Regional Pain Syndrome
DH	Department of Health
EAC	External Assessment Centre
EBM	Evidence based medicine
FBSS	Failed back surgery syndrome
FDA	Food and Drug Administration (USA)
GAF	Global Assessment of Functioning
HF10	High frequency SCS therapy at 10kHz (Senza HF™ technology)
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IPG	Implantable pulse generator
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
ODI	Oswestry Disability Index
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMS	Patient reported outcome measures
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
RCT	Randomised Controlled Trial
SAE	Serious adverse events
SCS	Spinal cord stimulation
SD	Standard deviation
SEM	Standard error of mean
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual Analogue Scale
vs	Versus

1 Executive Summary

Senza HF10 therapy is a novel spinal cord stimulation (SCS) technology that utilises high frequency (10 KHz) neuromodulation rather than low frequency (typically 40 to 60Hz) used by traditional SCS. It is intended for use in people with chronic, refractory, neuropathic pain of the back and/or legs, as described in recommendation 1.1 of NICE Technology Assessment 159 (2008) (TA 159). The company provided a high-quality submission that clearly defined the scope of the decision problem, and used this in their literature search strategy and throughout the submission.

The company identified seven clinical studies reported in nine peer-reviewed papers. All studies were within scope and generalisable to the NHS except one, which the EAC excluded. The EAC did not identify any other relevant clinical studies. The pivotal study was the non-inferiority SENZA-RCT (n = 198), which compared Senza HF10 therapy with traditional low frequency SCS with a 2-year follow up (Kapural *et al.*, 2015; Kapural *et al.*, 2016b). The results reported a statistically significant improvement in both leg and back pain with Senza HF10 compared with low frequency SCS. Senza HF10 was also associated with significant improvements in related disabilities and patient satisfaction. The EAC considered that although the RCT was subject to some potential sources of bias, the large and sustained comparative benefit was attributable to Senza HF10 therapy. The level of benefit was broadly supported by evidence from single-armed observational data. The patient groups included in these studies matched the scope, hence the results should generalise to the UK setting provided it is used in the same way.

The company provided an executable *de novo* economic model which was an adapted cost utility analysis previously used to inform TA 159. The EAC was satisfied that the model and the majority of its inputs were robust and accurately reflected the important economic considerations. In the base case over 15 years, Senza HF10 was found to save costs of £7,755 and £4,795 compared with non-rechargeable and rechargeable low frequency SCS systems respectively. The main driver of cost saving was improved pain relief resulting in lower medical costs, but there was material uncertainty on the parameter value used for these costs in the model. The direction of the results was unchanged using extensive deterministic sensitivity analysis except under assumptions the EAC considered were relatively implausible. The results were also robust to probabilistic sensitivity analysis, which indicated Senza HF10 was cost saving in around three quarters of iterations.

In summary, the EAC considered there was good evidence from a comparative RCT that Senza HF10 improves clinical outcomes compared with traditional low frequency SCS and that this generalises to NHS patients. Additionally, Senza HF10 therapy is likely to be cost saving to the NHS.

2 Background

Throughout this report, the EAC makes reference to specific sections within the company's submission, which is a separate document. Where the EAC cites clinical experts, further information can be obtained from the EAC external correspondence log (NYEAC, 2017).

2.1 Overview and critique of company's description of clinical context

The company provided a background review of the technology and its principal comparator in Section 2.2 of the submission. A review of the clinical context of the technology (i.e. its place in the current patient pathway) was provided in Section 2.3, and the relevant national guidelines were described in Section 2.4. The EAC considers these sections were well written, accurate, and informative. The following EAC summary is intended to add clarification to the company's description of the clinical context.

2.1.1 The technologies

In the mid-1960s, the gate control theory of pain postulated how electrical stimulation of neural pathways carrying non-painful signals could influence or dampen the conduction of noxious (painful) nerve signals (Melzack and Wall, 1965). This research directly led to the spin-off technology of low frequency spinal cord stimulation (SCS) as a means to reducing the sensation of chronic pain. During low frequency SCS, electrical stimulation is delivered by placement of electrodes in the epidural space of the spinal cord near the region that supplies nerves to the painful area. For leg and lower back pain, this is typically at the lower thoracic vertebral levels. The electrodes are connected to a compact neurostimulator implanted subcutaneously. The electrode is powered by an internal battery that can be rechargeable or non-rechargeable (see [Section 2.1.2](#)). Although the design and surgical procedures of low frequency SCS have evolved iteratively, the fundamental principle and physical parameters have remained largely unchanged over four decades.

Low frequency SCS has been found to be most effective in the treatment of chronic neuropathic pain, rather than nociceptive pain, and its use has become widespread, such that an estimated 24,000 devices are now implanted each year globally (Linderoth and Foreman, 2017). However, despite its widespread use, the fundamental mode of action of SCS is still poorly understood and proposed mechanisms are regarded as hypothetical (British Pain Society, 2009). Additionally, as its invention and introduction essentially predates the widespread application of Evidence Based Medicine (EBM), the magnitude of clinical effectiveness of SCS has not been fully established. In particular, there has been a lack of randomised controlled trials

(RCTs) utilising a control arm to estimate the size of the placebo effect during treatment.

The absence of published placebo controlled studies may in part relate to the methodological difficulty of achieving blinding, because low frequency SCS induces a detectable paraesthesia covering the area of the affected dermatomes, thus making it hard to mask patients and assessors. Paraesthesia is often poorly tolerated by the patient. An additional problem is it can trigger involuntary movement (jolting) following postural change; thus driving and operation of heavy machinery is contraindicated.

More recently, at least two new SCS technologies have been developed that provide pain relief without associated paraesthesia. These are the Burst SCS system (St Jude Medical), which reduces paraesthesia, and the high frequency Senza system, which eliminates paraesthesia (De Ridder *et al.*, 2015); this assessment concerns the latter technology. Senza high frequency SCS operates at a frequency of 10 kHz and is known as HF10™ therapy (henceforth called Senza HF10 in this document). This frequency is several magnitudes higher than traditional SCS (which operate in the Hz range), and no sensation is detectable to the patient. A major advantage of SCS HF10 therapy is that, because it does not induce paraesthesia, it is well tolerated and does not affect tasks such as driving.

The mechanism of action of high frequency SCS is currently not well understood, but, as the HF10 frequency is well above the firing rates supported by most neurons, it is believed to be substantially different to traditional low frequency SCS. Several hypotheses have been proffered. These include that HF10 induces a “depolarisation block”; HF10 stimulation induces desynchronisation of neural signal from neurons firing in synchronicity; and the “membrane integration” hypothesis, where the temporal summation of neurons are disrupted (Linderoth and Foreman, 2017; De Ridder and Vanneste, 2016). Research into the phenomenon of high frequency inducing analgesia is on-going using animal (Shechter *et al.*, 2013) and computer (Lempka *et al.*, 2015) models.

Some of the key differences between the intervention described in this report, the Senza HF10 system, and its comparator, low frequency SCS, are described in [Table 2.1](#).

Table 2.1. Comparison between Senza HF10 therapy and low frequency SCS.

	Senza HF10 therapy	Traditional low frequency SCS
Historical development	Rationale for development unclear. CE marked in 2010, gained FDA approval in May 2015.	Developed in late 1960s as a direct spin-off from Gate Control theory. Over 40 years of use.
Technical parameters*	Frequency: 10 kHz Pulse width: 30 μ s Amplitude: 1 to 5 mA.	Frequency: 40 Hz Pulse width: 400 μ s Amplitude: 4 to 6 mA.
Mechanism of action	Not known at present. Inhibits nociceptive and neuropathic pain components.	Not yet fully understood, mainly acts on neuropathic pain.
Simulation trial required?	Yes, with aim of 50% pain reduction.	Yes, pain reduction through induction of paraesthesia.
Implant procedure	Lead placement under anatomical landmarks. Patients under conscious sedation.	Leads placed on vertebra according to patient feedback on paraesthesia coverage. Intraoperative programming and lead adjustment.
Paraesthesia induction	No	Yes**
Able to drive and operate machinery?	Yes	No
Rechargeable and non-	Only available as	Both technologies

	Senza HF10 therapy	Traditional low frequency SCS
rechargeable battery (see below)	rechargeable	available
Principal comparative clinical evidence	One RCT***	Two RCTs***
<p>References: (Russo and Van Buyten, 2015; Linderoth and Foreman, 2017; De Ridder <i>et al.</i>, 2017; Deer <i>et al.</i>, 2014)</p> <p>* 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 waveform in which pulses are delivered at a consistent frequency, pulse width, and amplitude (although these parameters vary by device type).</p> <p>** All patients feel paraesthesia, but it is only unpleasant or intolerable in a proportion of these.</p> <p>*** See Table 2.3.</p>		

2.1.2 Rechargeable and non-rechargeable SCS

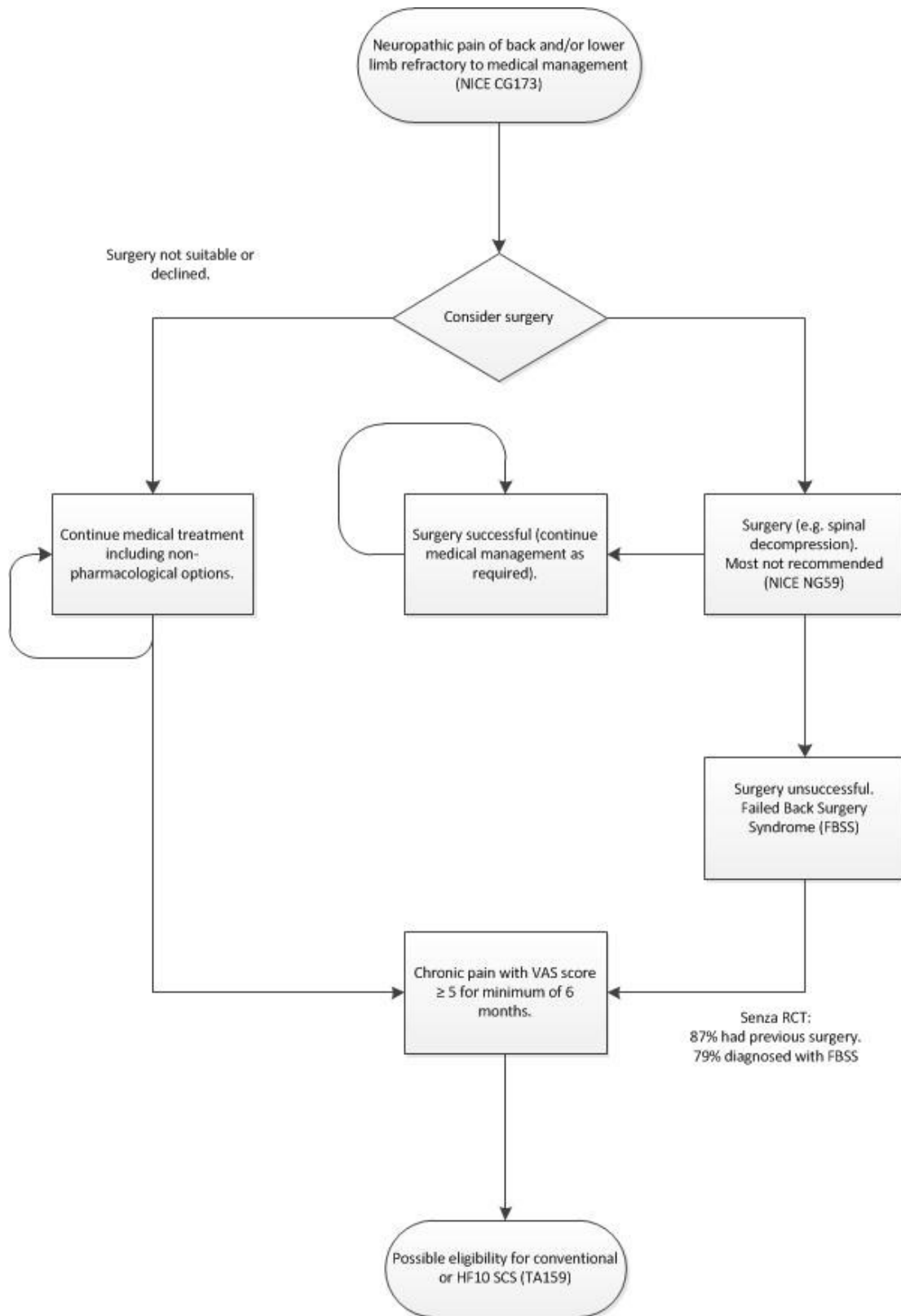
Senza HF10 technology utilises a constant high frequency field which results in a significant draw from the battery. Senza HF10 therapy is also typically used constantly by the patient, including during sleep. For these reasons, it necessarily requires a rechargeable battery. Traditional low frequency SCS on the other hand requires significantly less energy to operate. This technology is available with both rechargeable and non-rechargeable formats. Non-rechargeable options require more frequent replacement than their rechargeable counterparts, and are probably more costly in the longer-term (Hornberger *et al.*, 2008), but are otherwise regarded as equivalent technologies. In the UK, non-rechargeable technologies are currently thought to be used more extensively than their rechargeable equivalents (NYEAC, 2017).

2.1.3 Patient pathways

The patient pathways for chronic back and leg pain of neuropathic origin are described in Section 3.1 of the company's submission. The EAC agrees that this is an accurate description and has illustrated the patient pathway in [Figure 2.1](#).

Most patients who are indicated for SCS have had previous back surgery, which has often resulted in failed back surgery syndrome (FBSS). This a term used to define an unsatisfactory outcome of a patient who has undergone spinal surgery, irrespective of type or intervention area, with persistent pain in the lumbosacral region with or without it radiating to the leg (Bordoni and Marelli, 2016). The underlying cause of FBSS is due to iatrogenic effects such as the development of scar tissue, nerve damage or weakening of physical structures. In these patients, implanted SCS represents a third-line treatment option of last resort. Some patients may undergo SCS without prior surgery, but feedback from clinical experts (NYEAC, 2017) and the population enrolled into the SENZA-RCT study, suggests these are a minority (Kapural *et al.*, 2015).

Figure 2.1. *Patient flow algorithm for patients with severe, chronic back and leg pain of neuropathic origin.*



2.1.4 Key guidelines

Key UK guidelines relevant to the submission and this assessment report are listed in [Table 2.2](#). The most important guideline in this is NICE TA 159 (NICE, 2008).

Table 2.2. *List of principal UK guidelines.*

Guideline	Scope and relevance
<p>NICE TA 159. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (NICE, 2008).</p> <p>See Section 2.1.5.</p>	<p>Key NICE recommendations on use of low frequency SCS.</p> <p>Evidence base from technical assessment report (Simpson <i>et al.</i>, 2008).</p> <p>Published prior to development of HF10 system.</p>
<p>Spinal cord stimulation for the management of pain:</p> <p>British Pain Society guidelines (British Pain Society, 2009)</p>	<p>Consensus document prepared on behalf of the British Pain Society in consultation with the Society of British Neurological Surgeons.</p>
<p>NICE CG173. Neuropathic pain – pharmacological management (NICE, 2017a)</p>	<p>Recommendations for the pharmacological management of neuropathic pain. Covers management prior to surgery or consideration for SCS therapy.</p>
<p>NICE NG59. Low back pain and sciatica in over 16s: assessment and management (NICE, 2016).</p>	<p>Includes recommendations for assessment of back pain and sciatica and non-invasive and invasive (surgical) treatment.</p>
<p>NICE overview on neuropathic pain (NICE, 2017b)</p>	<p>Overview of NHS patient pathway for the management of neuropathic pain.</p>

2.1.5 NICE TA 159

The NICE technology appraisal *Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin* was published in October 2008 (NICE, 2008). It has since been reviewed in 2014 with no important changes in recommendations or updates to the evidence base, and placed on the static list (NICE, 2013). This technology appraisal was informed by an Assessment Report authored by the School of Health and Related Research (SchHARR) at Sheffield University (Simpson *et al.*, 2008). The TA 159 Assessment Report included a systematic review and cost utility analysis; the decision analytic model used in the latter has been used in later publications and was the basis of the *de novo* model of the company's submission (see [Section 4](#)).

The estimate of clinical and cost-effectiveness of traditional low frequency SCS was largely 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 predominantly neuropathic leg pain with or without back pain who had failed back surgery syndrome (FBSS), and compared the use of low frequency SCS with conventional medical management (CMM) (Kumar *et al.*, 2007). The primary outcome of this trial was the proportion of patients achieving 50% or more reduction in leg pain as measured using the visual analogue scale (VAS) at 6 months. This was achieved in significantly more patients in the low frequency SCS group (48%) than the CMM control group (9%, $p < 0.01$).

The trial by North *et al.* (2005) was designed to compare the efficacy of low frequency SCS with reoperation in patients with FBSS and predominant leg pain (North *et al.*, 2005). Out of 99 identified candidates for SCS, 60 were randomised ($n = 30$ to each arm), and 50 were treated. This trial allowed crossover of patients to either arm, which occurred in 14 patients (54%) initially receiving surgery and 5 (21%) who received low frequency SCS. The primary "success" outcome was a composite of at least 50% pain relief (as measured by VAS) and patient satisfaction. Using intention to treat (ITT) analysis, successful response to low frequency SCS was higher (47%) than in the reoperation group (12%).

The EAC has critically appraised these studies for completeness (see [Appendix B](#)). The EAC found that the studies were of generally low methodological quality, particularly the study by North *et al.* (2005) which was considered to be at high risk of bias in every domain. Both studies were limited by a lack of blinding which was not possible due to the interventions being assessed; similarly it was not possible to investigate the additional efficacy of the technologies compared with a sham device. Both studies were relatively small with limited follow up, and extensive cross over in the trials meant that interpretation of results was difficult.

A comparison of the two RCTs on low frequency SCS used to inform TA 159 and the SENZA-RCT (the principal clinical evidence used in the company's submission) are reported in [Table 2.3](#).

Table 2.3. *Comparison of scopes of RCTs used to inform TA 159 and the SENZA-RCT.*

Domain	PROCESS study (2007) (Kumar et al., 2007)	North et al. (2005) (North et al., 2005)	SENZA-RCT (Kapural et al., 2015)
Trial type	Open label superiority RCT	Open label superiority RCT	Open label non-inferiority RCT
Population (study Inclusion criteria)	All patients had neuropathic leg pain with or without back pain secondary to FBSS.	Patients with predominant leg pain with one or more prior episodes of surgery and eligible for further surgery. Pain refractory to conservative care, with concordant neurological, tension, and/or mechanical signs and imaging findings of neural compression.	All patients had back and/or leg pain of ≥ 5 out of 10 cm on VAS for ≥ 3 months. Most patients (around 90%) had FBSS.
Intervention	Synergy LF SCS (Medtronic)	Permanent LF SCS. Resume electrode, X-trel or Itrel pulse generator; (Medtronic)	Senza HF10 therapy (Nevro).
Comparator	Conventional medical treatment	Surgery. Laminectomy and/or foraminotomy and/or discectomy in all patients with or without fusion.	LF SCS (Precision Plus system, Boston Scientific).
Sample size	214 assessed for eligibility 100 randomised: intervention (n=52), comparator (n=48).	99 patients eligible. 60 randomised to intervention (n=30) and comparator (n=30).	241 as assessed for eligibility for treatment. 101 assigned to Senza HF10 97 assigned to LF SCS.
Primary outcomes	Proportion of patients achieving at least 50% leg pain relief at 6 months. Secondary outcomes were improvement in back and leg pain.	"Success": at least 50% pain relief and satisfaction with treatment.	Proportion of "responders" at 3 months post-device activation ($\geq 50\%$ reduction in back pain VAS).

Domain	PROCESS study (2007) (Kumar et al., 2007)	North et al. (2005) (North et al., 2005)	SENZA-RCT (Kapural et al., 2015)
Key secondary outcomes	Improvement in back and leg pain. HRQoL. Functional capacity (ODI). Change in the use of pain medication and non-drug pain therapy. Patient satisfaction with treatment. Incidence of adverse effects.	Proportion crossing over to other arm. Improvement in daily activities, neurological status and medication use.	Pain reduction as measured by VAS. Proportion of “remitters”. Functional disability (including ODI). Patient satisfaction. Ability to drive and operate machinery. Adverse events.
Follow up	Primary efficacy: 6 months Safety: 12 months	≥2 years	2 years
Abbreviations. FBSS: failed back surgery syndrome; HRQoL: health related quality of life; LF: low frequency; ODI: Oswestry Disability Index; VAS: visual analogue scale.			

2.2 Critique of company’s definition of the decision problem

2.2.1 Scope of the decision problem

The company reported the statement of the decision problem in Table 1 of the submission. As reported in [Table 2.4](#), there were no important deviations from the published scope (NICE, 2017c).

Table 2.4 Critique of company's definition of the decision problem.

Decision problem	Company's submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	Patients undergoing spinal cord stimulation for chronic pain in line with NICE Technology Appraisal 159.	Y	<p>Patient population is clearly defined by that in recommendation 1.1 in TA 159 (NICE, 2008). This is “adults with chronic pain of neuropathic origin who:</p> <ul style="list-style-type: none"> • continue to experience chronic pain (measuring at least 50 mm on a 0–100 mm visual analogue scale) for at least 6 months despite appropriate conventional medical management, and • who have had a successful trial of stimulation as part of the assessment specified in recommendation 1.3” [involvement of multidisciplinary team]. <p>Note: evidence from TA 159 was mainly derived from patients with back and/or leg pain (subsequent to FBSS). There is a paucity of evidence for the use of Senza HF10 in conditions affecting the upper limbs, head, and neck (which requires lead placement in the cervical vertebral region). Additionally, the company restricted their literature search to back and leg pain (Section 3.1).</p>

Decision problem	Company's submission	Matches decision problem? (Y/N/partially)	EAC comment
			Therefore for practical purposes, the population is restricted to patients with neuropathic pain of the lower back and/or legs.
Intervention	HF10™ therapy using the Senza™ spinal cord simulation system.	Y	Intervention is clearly defined. HF10 therapy employs the following technical parameters: short-duration pulse width (30 µs); high-frequency (10 kHz); low-amplitude (1 to 5 mA) (Kapural <i>et al.</i> , 2015).
Comparator(s)	Low frequency spinal cord stimulation (up to 1200 Hz).	Y	<p>Most commercial systems employ a stimulation frequency of 40 to 60 Hz. Frequencies of 300 Hz or less induce paraesthesia detectable to the patient (Schade <i>et al.</i>, 2010).</p> <p>The EAC notes that in TA 159, individual low frequency SCS devices were not compared with each other; that is there was an assumption of equivalence of the traditional SCS technologies (NICE, 2008).</p>
Outcomes	<p>The outcome measures to consider include:</p> <ul style="list-style-type: none"> • Pain scores (for example VAS score) 	Partially	Outcomes were all included and consistent with the published scope with the exception of the outcomes <u>underlined</u> . The company elected to omit these healthcare resource use outcomes from their decision problem analysis. The reasons for omission were because, although the company cited anecdotal evidence in support of these outcomes, the company did not identify objective data from published trials.

Decision problem	Company's submission	Matches decision problem? (Y/N/partially)	EAC comment
	<ul style="list-style-type: none"> • Duration of pain relief • Patient satisfaction relating for example to frequency of battery recharging. • Health-related quality-of-life • Functional disability measures e.g. disability Index Score, Oswestry Disability Index and functional improvement including ability to drive and perform work-related activities • Opioid and other analgesic use • Device-related adverse events 		<p>The EAC acknowledges that the omission of these outcomes is reasonable. The EAC also notes that an absence of published quantitative evidence, which is often lacking in the literature for healthcare resource use outcomes, does not suggest evidence of negative outcomes.</p> <p>Both company and EAC literature searches were broad and did not discriminate by outcome (see Section 3.1 and 3.2).</p>

Decision problem	Company's submission	Matches decision problem? (Y/N/partially)	EAC comment
	<ul style="list-style-type: none"> • <u>Implantation time in theatre</u> • Incidence of paraesthesia • Reason for implant removal • <u>Follow up appointments including attendance at pain clinics</u> • <u>Staff conducting device programming</u> 		
Cost analysis	<p>Comparator(s):</p> <ul style="list-style-type: none"> • Low frequency spinal cord stimulation (up to 1200 Hz) <p>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</p>	Y	The cost comparator fully matches the comparator identified for clinical effectiveness, which is appropriate.

Decision problem	Company's submission	Matches decision problem? (Y/N/partially)	EAC comment
	<p>consequences between the technologies being compared. This will include the trial and permanent implantation phases of the care pathway.</p> <p>Sensitivity analysis will be undertaken to address uncertainties in the model parameters.</p>		
Subgroups	<ol style="list-style-type: none"> 1. Previous back surgery / failed back surgery syndrome. 2. Chronic pain involving the limbs 3. Chronic pain involving the back 4. Complex regional pain syndrome 	N	<p>The company elected to omit these subgroups from consideration in their analysis of the decision problem. The reasons stated were that available clinical evidence indicated there was no significant difference in outcomes between these subgroups. In the case of complex regional pain syndrome (CRPS), there was no comparative evidence available.</p> <p>The EAC acknowledges these omissions. As literature searches do not discriminate by subgroup, individual subgroups are considered separately only when reported and there is a clinically important distinction.</p>

2.2.2 Special considerations, including issues related to equality

The final scope for this assessment stated “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 their ability to do normal daily activities. Disability is a protected characteristic under the Act” (NICE, 2017c).

No selective advantages or disadvantages were identified, nor the potential for the guidance to cause unlawful discrimination or not promote equality. No specific issues were identified that needed further consideration for the development of this guidance.

3 Clinical evidence

3.1 Critique of and revisions to the company’s search strategy

In sections 7.1 and 8.1 of the submission the company reports the search methodology used to identify clinical evidence. In section 5.1 the company also report a search for ongoing studies. The search methods reported in the submission do not contain sufficient detail to be certain of the exact search methods used, but enough information was provided for the EAC to make an informed judgement as to how the searches were conducted, and the company’s searches were re-run on this basis. The re-run company’s searches retrieved 583 records. After de-duplication, 314 records remained. The company’s search methods had some limitations which could potentially impact on search sensitivity. The EAC therefore also conducted a *de novo* literature search. The EAC searches retrieved 1446 records. After de-duplication (within-set, and against the results of the re-run company’s searches) 637 records remained. Of the 637 records, 244 were identified as conference-related publication types from Embase and the Conference Proceedings Citation Index - Science database. Following discussion with NICE, it was agreed that conference-related publication types would be excluded from the EAC report, leaving 393 records for assessment. A full critique of the company’s search methods is provided in [Appendix A1](#). A description of the methods used in the re-running of the company’s searches is provided in [Appendix A2](#). A description of the EAC *de novo* search methods is provided in [Appendix A3](#).

3.2 Critique of the company’s study selection

The study selection applied by the company (Table 5 of the company’s submission) was generally consistent with the scope specified by NICE and

identified studies according to the relevant population, intervention and outcomes.

The company applied a constraint to the population in selecting 'Patients with chronic neuropathic pain in the legs and/or back', whereas NICE had specified, in their Statement of the decision problem (Table 1 of the company's submission), that the population in scope was 'Patients undergoing spinal cord stimulation for chronic pain in line with NICE Technology Appraisal 159'. NICE TA 159 did not exclude patients with neuropathic pain in the upper limbs and neck and these are not explicitly excluded in the Senza device Indications for Use (Nevro Corp, 2015):

"The Nevro™ SCS system is intended to aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following:

1. Failed back surgery syndrome (FBSS)
2. Intractable low back pain
3. Leg pain"

The EAC has thus concluded that any conclusions or NICE recommendations drawn from this assessment report should be limited to populations with leg and back pain of suspected neuropathic origin only.

The company also applied a limit on study design to patient numbers ≥ 15 . The EAC, in repeating the company's literature search, applied a more conventional lower limit to patient numbers of $n \geq 10$, in order to check that no potentially useful studies were excluded by this constraint. The EAC did not apply any limit on outcomes, whereas the company specified a list of nine outcomes for their selection of included studies. The EAC also flagged any systematic reviews, economic studies, quality of life studies and case reports of adverse events, as potentially useful evidence for other sections of this assessment report.

The company devised and performed one structured literature search for published evidence from 2006 onwards, reflecting the earliest existence of Nevro Corporation. A language limit was also applied to studies written in English. Both of these eligibility criteria were considered appropriate by the EAC. The company additionally hand searched internal records for unpublished data, but chose to exclude conference abstracts from the primary evidence presented, although making 46 such records available to NICE and the EAC for information. The company's systematic literature review and hand searches are summarised in a schematic in Figure 4 of the company's submission.

The EAC presents its independent study selection from a re-run of the company search strategy, plus the additional EAC search strategy, in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (Moher *et al.*, 2009) in Figures A1.1 and A1.2 in [Appendix A4](#). The selection of records was conducted based on title and abstract by two reviewers independently. Full papers of the studies selected at first sift were retrieved and reviewed by one reviewer, with consensus reached on reasons for inclusion and exclusion with the second reviewer.

3.3 Included and excluded studies

The company included seven studies reported in nine papers in Table 6 of the submission. One of these was excluded by the EAC on the basis of population and reported outcomes (De Carolis *et al.*, 2017), leaving six studies included by the EAC ([Table 3.1](#)).

The application by the EAC of a lower limit on study size ($n \geq 10$, rather than the company's choice of $n \geq 15$) identified a further three potentially relevant studies. However, on full paper review, these were excluded from further consideration on the following basis:

- Comparator not applicable. One study, reported in two papers, compared Senza HF10 therapy with Burst SCS (St. Jude Medical). This system utilises a frequency of 500 Hz with a repetition rate of 40 Hz and, unlike traditional SCS, does not induce paraesthesia (Linderoth and Foreman, 2017). Additionally, only eight patients were included in the Senza HF10 therapy arm (Muhammad *et al.*, 2017; Kinfé *et al.*, 2016).
- Population not applicable. One small retrospective case series reported data on eleven patients (Al-Kaisy *et al.*, 2015). However, there was a predominance of patients with upper limb and hand pain ($n = 8$), which have been excluded for practical reasons ([Table 3.1](#)).

Therefore no additional studies in scope were found in either the EAC re-run of the company's search strategy (Figure A1.1 in [Appendix A4](#)), or the additional EAC search strategy (Figure A1.2 in [Appendix A4](#)).

Table 3.1. Overview of EAC's included studies.

Included studies	Design and intervention(s)	Participants and setting	Follow up	Outcomes	Withdrawals	EAC Comments
Comparative experimental study (RCT)						
SENZA-RCT (Kapural et al., 2016c; Kapural et al., 2015)	Multicentre open-label RCT comparing Senza HF-10 vs. LF SCS (Precision Plus System; Boston Scientific) intervention ● comparator ●	10 pain centres, USA. 198 randomised (101 Senza HF vs 97 low frequency SCS). Inclusion criteria severe, chronic back and/or leg pain (ODI 41 to 80 and VAS >5cm) for minimum 3 months. Most patients (77%) had FBSS. ●	Follow up conducted at post-procedure procedure, and at 3, 6, 9, 12, 18 24 months.	<u>Primary endpoint:</u> VAS for back and leg pain at 3 months <u>"Key" outcomes:</u> VAS for back and leg pain at other follow up times ODI Global Assessment of Functioning Subject satisfaction. <u>Other outcomes:</u> Proportion responders (≥50% reduction in pain VAS) Proportion "remitters": (VAS pain score ≤2.5) Opioid analgesic use Study related AE ●	241 assessed for eligibility, 43 excluded at screen. 198 randomised. <u>Senza HF10</u> 101 assigned 97 trialled 90 permanent implant 89 followed up 12 months 85 followed up 24 months <u>LF SCS</u> 97 assigned 92 trialled 81 permanent implant 80 follow up 12 months 71 follow up 24 months	Non-inferiority trial with superiority outcomes reported. No sham control arm (placebo) used. Patients, clinicians, and investigators not blinded. Arms not exactly equivalent at baseline Loss to follow up substantial using ITT analysis (overall 21% loss to follow up after 24 months).
Comparative uncontrolled study						

Included studies	Design and intervention(s)	Participants and setting	Follow up	Outcomes	Withdrawals	EAC Comments
“Before and after” study (Tiede et al., 2013)	Non-randomised “before and after study”. Patients received commercially available LF SCS first and then switched to “investigational external trial stimulator” incorporating Senza HF technical parameters. Intervention ● Comparator ●	Multicentre study in USA. Patient (n=25) had severe chronic back pain and were already confirmed as candidates for LF SCS. Most patients (92%) had FBSS. ●	Short-term study with data collection at baseline, after treatment with LF SCS (4 to 7 days) and HF SCS (4 days).	Overall pain VAS Back pain VAS Patient preference ●	One patient withdrew from study.	Investigational study which helped to inform protocol development. Order of device use was not randomised meaning it is not possible to infer superiority of one device over another.
Non-comparative observational studies						
SENZA-EU study (Al-Kaisy et al., 2014; Van Buyten et al., 2013)	Observational case series Senza HF10 therapy ●	Patients (n=83) recruited from two centres (Belgium and UK). Eligibility criteria was diagnosis of back pain with/without leg pain minimum average VAS score of 5 in previous 30 days, and failure to respond to CMM previous 6 months. Most patients (81%) had FBSS. ●	Follow up at baseline, post-procedure, and at: 1 month 3 months 6 months 12 months 24 months	VAS scores for back, leg, and overall pain. Sleep disturbance (number of awakenings) ODI Patient satisfaction Study related AE ●	83 patient underwent trial 72 patients successful trial (permanent implant) Follow up (patients): 1 month: 72 3 months: 70 6 months: 72 12 months: 68 24 months: 65	Single armed study generalisable to population in scope. Reporting quality high.

Included studies	Design and intervention(s)	Participants and setting	Follow up	Outcomes	Withdrawals	EAC Comments
<i>Retrospective case series (Russo et al., 2016)</i>	<i>Retrospective observational case series Senza HF10 therapy</i> ●	<i>Patient data (n=256) from three Australian pain centres. No formal inclusion or exclusion criteria. Patients had a range of chronic intractable pain distributions including head and neck, or not recorded. Patients were not suitable candidates for LF SCS, or had failed treatment with LF SCS.</i> ●	<i>Retrospective analysis of routine data collected at base-line, post-trial, 3 months, and 6 months post implant.</i>	<i>NPRS ODI (from two sites) Sitting tolerance</i> ●	<i>N/A Incomplete outcome data.</i>	<i>Retrospective nature of study reduces inferences that can be made. Patient population not compatible with scope.</i>
<i>Case series (Rapcan et al., 2015)</i>	<i>Prospective case series. Intervention was Senza HF10 procedure.</i> ●	<i>Patients (n=21) recruited from four Slovak centres. Patients had primary diagnosis of back pain with or without leg pain. Pain was severe and chronic (mean duration 7.8 year).</i> ●	<i>Follow up was: Baseline Immediate post procedure. 3 months. 6 months 9 months 12 months</i>	<i>Pain (back and leg) measured by VAS "Performance status" [disability measure] Patient satisfaction Opioid consumption</i> ●	<i>No loss to follow up reported.</i>	<i>Small study of poor methodological quality.</i>

Included studies	Design and intervention(s)	Participants and setting	Follow up	Outcomes	Withdrawals	EAC Comments
Case series (Al-Kaisy et al., 2017)	Prospective case series. Senza H10 therapy. ●	Single centre study (Guy's hospital, UK). Patients naïve to surgery had predominant back pain which was chronic and severe. (n=21) ●	Follow up was: Baseline End of trial 3 months 6 months 9 months 12 months	Pain intensity using VAS. ODI. HRQoL (EQ-5D) SF-36 Global impression of change Patient satisfaction Opioid use Sleep quality Work status AE ●	20/21 had successful trial. Of these, no patients lost to follow up.	Study limited by small sample size. Well reported with thorough outcomes.
<p>Abbreviations. AE: adverse effects; EQ-5D: Euroqol-5D; FBSS: Failed Back Surgery Syndrome; HF: high frequency; HRQoL: quality of life LF; low frequency; N/A: not applicable; NPRS: numerical pain rating scale; ODI: Oswestry disability index; SF-36: 36 Item; Short Form Health Survey v2; VAS: visual analogue scale.</p> <p>● Fully matches scope ● Partially matches scope ● Does not match scope</p>						

3.4 Overview of methodologies of all included studies

The company reported the methodology of the included studies in section 7.4.1 of the submission. A description of the SENZA-RCT (Kapural *et al.*, 2015; Kapural *et al.*, 2016c) is reported in Table 7 of the submission. The observational studies (Al-Kaisy *et al.*, 2017; Al-Kaisy *et al.*, 2014; Rapcan *et al.*, 2015; Russo *et al.*, 2016; Tiede *et al.*, 2013; Van Buyten *et al.*, 2013) included by the EAC are described in Tables 8 to 12 of the submission. The EAC has reviewed the information presented in these tables and did not identify any major discrepancies in transcription from the published literature.

The EAC has summarised the methodologies of all included studies in [Table 3.2](#). The following section provides a narrative summary of the included studies. Throughout this report, particular attention is given to the SENZA-RCT study as this trial provides the key comparative evidence to support the technology's efficacy and safety compared with the established comparator, low frequency SCS.

SENZA-RCT study

The SENZA-RCT was a pivotal multicentre study submitted to the US Food and Drug Administration (FDA) as part of product licensing in the USA. It was designed as a non-inferiority trial that compared the use of Senza HF10 therapy with low frequency SCS (Precision Plus System by Boston Scientific) in the treatment of recalcitrant back and leg pain of suspected neuropathic origin. Of the 241 participants assessed for eligibility, 198 were randomised to receive Senza HF10 (n = 101) or low frequency SCS (n = 97). Follow up was reported in one peer reviewed published paper at 12 months (Kapural *et al.*, 2015) and one at 24 months (Kapural *et al.*, 2016c).

The SENZA-RCT study was well-matched with the scope of the decision problem (NICE, 2017c). The population recruited had neuropathic pain with multiple aetiologies and symptoms. Most patients (87%) had received previous back surgery which had failed to adequately treat pain symptoms, with 77% being recorded as having FBSS. This population appears to reflect those of the two RCTs (North *et al.*, 2005; Kumar *et al.*, 2007) that were used to inform TA 159 (NICE, 2008), although in the earlier studies all patients had FBSS (see [Table 2.3](#)). The intervention was the Senza device implementing HF10 therapy (30 µs pulses delivered at 10,000 Hz with mean amplitude of 1.6 to 3.8 mA), which was in accordance with the scope.

The comparator was a commercially available low frequency SCS system that matched the scope. The trial reported a number of outcomes which were also compatible with those described in the scope, and follow up of 2 years gave

some insight into the persistence of effect over a medium, rather than long-term, time horizon.

Observational studies

Six single-armed studies were identified as relevant by the company, of which five were included by the EAC (see [Section 3.3](#)). Most of the studies were observational case series of the Senza HF10 therapy system, and all were reported fully in peer-reviewed journals. One experimental study had a “before and after” design that compared use of Senza directly after use of low frequency SCS (Tiede *et al.*, 2013); however, the order of intervention was not varied or randomised. One study (SENZA-EU) was a relatively large prospective case series (n = 83) set in Belgium and the UK with 24 months follow up (Al-Kaisy *et al.*, 2015; Van Buyten *et al.*, 2013). Two were smaller prospective case series set in Slovakia (Rapcan *et al.*, 2015) and the UK (Al-Kaisy *et al.*, 2017). One study was a relatively large (n = 256) retrospective analysis of patient data (Russo *et al.*, 2016).

In general, the studies adequately matched the domains of the scope. The SENZA-EU study matched the scope in terms of population, as did the case series by Rapcan *et al.* (2015) and the before and after study by Tiede *et al.* (2013). The UK case series by Al-Kaisy *et al.* (2016) was restricted to surgically naïve patients, which is a subgroup of the scope population. The study by Russo *et al.* (2016) included patients with head, neck, shoulder, and complex pain, as well as patients with previous failed low frequency SCS. The EAC considered that, although these patients were not technically out of scope, they formed a subgroup which was likely to have limited generalisability regarding most patients on the clinical pathway. All the studies reported relevant clinical and patient reported outcome measures (PROMS). However, the study by Tiede *et al.* (2013) was restricted to a very short timeframe and it was not possible to extrapolate results to reflect longer-term benefits which are clinically relevant.

3.5 Overview and critique of the company’s critical appraisal

3.5.1 Critique of the company’s critical appraisal

The company critically appraised all the included studies in Section 7.5.1, using the tools included in the submission template, which are based on the Critical Appraisal Skills Programme (CASP, 2017). The SENZA-RCT was appraised using the RCT checklist which is appropriate, in Table 16. The observational studies were appraised using the cohort study checklists (Table 17 to 21), which are not a good fit for single-armed studies of heterogeneous methodology.

The EAC noted that the company had thoroughly reported the methodology, strengths, and some of the limitations of the included studies. The EAC agreed with most but not all the statements made. The EAC has therefore independently critically appraised the studies in the following section.

3.5.2 EAC critical appraisal of included studies

SENZA-RCT

Internal validity

The EAC has critically appraised the RCT using the *Cochrane Collaboration's tool for assessing the risk of bias in randomized trials*. This is a standardised tool that is extensively used to assess the study quality of RCTs during the development of systematic reviews (Savovic *et al.*, 2014). Results of the EAC's appraisal are tabulated in [Appendix B](#) (Table B3).

The SENZA-RCT was a multi-centre, open label RCT that compared the efficacy and safety of Senza HF10 therapy with traditional low frequency SCS (Precision Plus System by Boston Scientific), with outcomes reported at 12 months (Kapural *et al.*, 2015) and 24 months (Kapural *et al.*, 2016c). The methodology and rationale for this trial had been previously published as a protocol on clinicalTrials.gov ([NCT01609972](#)) and as a conference abstract (Sitzman *et al.*, 2015).

The EAC considered there was a risk of selection bias. This was because the method of allocation concealment was not adequately described in the published papers, and because there were statistically significant differences in the groups with respect to baseline leg and back pain. Although the authors reported that *post hoc* analysis had indicated this baseline difference did not affect the results, it may signify there were unknown issues with the randomisation or allocation process.

The authors acknowledged that a limitation of the trial was that it was open-label, with patients, treating clinicians, assessors, and analysts all being aware of the treatment allocation. Although the EAC accepts that it would not have been possible to blind the patients to the treatment they were receiving (primarily because of the presence or absence of paraesthesia), this meant there was a high risk of performance and detection bias. This was particularly relevant because the outcomes were subjective, rather than objective (Higgins and Green, 2015).

The patient flow of the study was reported in the RCT manuscript (see Figure 5 of company's submission), with an apparently clear description of loss to follow up and reasons for this at each stage. As this loss was substantial (at

over 20%) and relatively uneven at 24 months, the EAC considered the risk of attrition bias was relatively high.

The published manuscripts (Kapural *et al.*, 2015; Kapural *et al.*, 2016c) state that “Primary end point analyses were performed on intention-to-treat (ITT, subjects receiving a randomization assignment), per protocol (PP, subjects completing a primary end point assessment), and permanent implant (PI, subjects passing a short-term screening trial and receiving a permanent SCS system) populations. For subjects who had a successful screening trial and received an IPG implant, the primary efficacy assessment occurred at 3 months post device activation. Subjects who did not have a successful trial phase were considered non-responders for the ITT and PP analyses.” Intention to treat (ITT) analysis is an appropriate approach to data analysis of RCTs (Gupta, 2011). However, upon careful analysis of the reported primary data, the EAC became aware that many of the results were reported using a cohort of patient numbers in each arm which did not correspond to any of the three defined populations in the published study subject flow diagram (n=92 for Senza HF10 therapy and n=87 for low frequency SCS). The only results clearly reported in the ITT cohort (largest denominator) were the adverse events; this included patients who were not even trialled for SCS. However, there was some evidence, from the primary outcome at least, that the selective reporting of different analyses did not affect the differential estimates of efficacy (evidenced in Figure 2 of published manuscript) (Kapural *et al.*, 2015). 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 (see [Section 3.7](#)).

The EAC noted that a power calculation was performed to inform the sample size required for measurement of the primary outcome and testing of the null hypothesis. This did not match the estimated sample size required that was reported in the trial protocol. The company has stated that this is because the sample size stated in the protocol took into account higher levels of patient attrition during the eligibility assessment than actually occurred (NYEAC, 2017). However, the rationale for the margin of inferiority used was not described in the published papers. Additionally, some outcomes, such as the proportion of “pain remitters” were defined on a *post hoc* basis. 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 fully report the inter- and intra-patient variability of responses over time. A number of secondary outcomes were reported with appropriate statistical methods for multiple comparisons employed. Overall, the EAC considered there was a high risk of reporting bias.

Overall, the EAC concluded that the SENZA-RCT study had some potential issues with internal validity, some of which, in particular the lack of patient blinding, were unavoidable. However, limitations of the trial and potential sources of bias should be taken in the context of the large and sustained effects reported (see [Section 3.6.3](#)).

External validity

The EAC considered that results from the SENZA-RCT were generalisable to patients eligible for treatment with low frequency SCS as described TA 159 (NICE, 2008). One difference in the population domain was that in the NHS, patients are only eligible for SCS if they have had pain refractory to CMM for a minimum of 6 months, whilst in the SENZA-RCT study the requirement for inclusion was 3 months or more. However, in reality the large majority of patients had had a diagnosis of pain for an extended period (mean of 13.0 years in Senza HF10 arm or 14.2 years in low frequency SCS arm). Otherwise, the heterogeneous mix of pain aetiologies, predominantly following unsuccessful back surgery, was consistent with recommendations 1.1 of TA 159 (see [Table 2.2](#)).

Single armed studies

The single armed studies are critically appraised in [Appendix B](#) (Table B4 to B8) using appropriate checklists for case series developed by the Centre for Reviews and Dissemination (CRD) (Centre for Reviews and Dissemination, 2009). Single armed studies are regarded as being of lower methodological quality and require either explicit comparisons with uncontrolled data sources (e.g. historical data) or implicit extrapolation for their interpretation (AHRQ, 2013).

The proof of concept “before and after” study was the only single-armed experimental study that made an explicit comparison with another intervention (low frequency SCS) (Tiede *et al.*, 2013). This was a small study restricted to short-term follow up (as leads were brought outside of the body). Although this is an entirely satisfactory design for a study at this point of the product cycle, the fixed temporal sequence of treatment with low frequency SCS used first, followed by Senza HF10 afterwards, means causation of effect cannot be solely attributed to the interventional technology with confidence.

The other single-armed studies were observational in nature and had no comparator group; thus only implicit interpretation is possible. The SENZA-EU study was a prospective case series conducted in the UK and Belgium and therefore generalisable to the NHS (Van Buyten *et al.*, 2013; Al-Kaisy *et al.*, 2014). It employed a relatively large sample size, and included follow up of relevant outcomes of up to 24 months. The Australian case series had a

relatively large sample size, but was retrospective in design and of low methodological quality (Russo *et al.*, 2016). This study is less generalisable to the UK setting as it did not employ inclusion or exclusion criteria for patient selection, patients had complex pain syndromes including the upper limbs, head, and neck, and patients were not candidates for, or had failed treatment with, low frequency SCS. The small prospective Slovakian case series (Rapcan *et al.*, 2015) was performed in an applicable heterogeneous population. In contrast, the small prospective UK case series was restricted to surgically naïve patients and thus may have limited generalisability (Al-Kaisy *et al.*, 2017).

The internal and external validity of the single-armed studies are summarised in [Table 3.2](#).

Table 3.2. *Summary of methodological quality and generalisability of single-armed studies.*

Study	Methodological quality*	Reporting quality**	Applicability to decision problem***	EAC comment
<i>SENZA-EU study (Al-Kaisy et al., 2014; Van Buyten et al., 2013)</i>	High	High	High	Larger study conducted in relevant population with 24 months follow up.
<i>“Before and after” study (Tiede et al., 2013)</i>	Low	Moderate	Moderate	Experimental study with very short term follow up.
<i>Retrospective case series (Russo et al., 2016)</i>	Low	High	Low	Patients not indicated for LF SCS. Included patients with complex pain syndromes of arms, head, and neck.
<i>Case series (Rapcan et al., 2015)</i>	Moderate	Moderate	High	Small study with non-validated outcomes.
<i>Case series (Al-Kaisy et al., 2017)</i>	High	High	Low	Patients were naïve to prior back surgery.

* Methodological quality *relative to studies of this type*. All single armed observational studies are subject to extensive sources of bias and confounding and are regarded low quality in the hierarchy of evidence.

** Reporting quality refers to how comprehensive the studies were described (e.g. whether

the detail would allow the study to be repeated).

*** Applicability concerns how the population recruited and intervention used relate to the decision problem.

3.6 Results

3.6.1 Critique of company's report of results

The company reported the results from their included studies in Section 7.6.1 of the submission. Results of each study were reported in detail as they appeared in the published literature, in tabular (Tables 22 to 37) and graphical format (Figures 7 to 17).

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-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).

The company also included data from a satisfaction feedback survey (unpublished) in section 7.6.3. These unpublished data could not be appraised, so have been excluded by the EAC from any further consideration in this assessment report.

The EAC has cross-referenced the company's tabulated results with each other and the original published data and, whilst a number of transcription errors were identified in the submission, including incorrect reporting of patient numbers (denominators) for some outcome measures, these do not impact upon the EAC assessment of the technology. Where possible, the EAC lead author has used data directly reported in the results sections of the published studies for reporting of outcomes in section 3.6.2 of this assessment report and these have been independently quality assured by a second EAC reviewer.

As the De Carolis *et al.* (2017) study was excluded from assessment by the EAC on the basis of population and reported outcomes, the company's report of these results was not independently checked (Table 37, company's submission, plus narrative summary statements in section 7.9.1, interpretation of the clinical evidence).

In addition, Table 23 of the company's submission (results from the SENZA-RCT) included some data from a conference poster which had not been selected for inclusion by the company or EAC (Amirdekfan *et al.*, 2016) or the

source material was otherwise not identified. These outcomes were therefore also excluded from EAC assessment (i.e. Table 23 results for: Mean improvement in GAF scores (SE); Sleeping and driving with the device turned on (%); Charging satisfaction (%) and Patient reliance on remote control (%)).

The EAC has also cross-referenced the claims made in the interpretation of the evidence in Section 7.9.1 of the company's submission. Again, minor transcription errors were identified by the EAC in this section, compared with the original published studies, but these had no bearing on the independent EAC assessment of the technology.

3.6.2. EAC's reporting of results

The EAC has reported results by outcome in the order listed in the scope of the decision problem and included relevant data from the included published studies. Tables and figures reported in the company's submission are not duplicated; rather tables are reported to compare results for compatible outcomes reported in multiple studies.

The principal study of interest was the SENZA-RCT study because this reported comparative data (Kapural *et al.*, 2015; Kapural *et al.*, 2016c). Secondary to this, the SENZA-EU observational study (Van Buyten *et al.*, 2013) was regarded as the highest quality single armed study, as it was prospective, had a relatively large sample size, and reported relevant outcomes at up to 24 months (Al-Kaisy *et al.*, 2014). The other studies were particularly limited by methodological quality or sample size, but relevant results are reported where appropriate. In particular, data from the study by the proof of concept study by Tiede *et al.* (2013) has been largely excluded because of the very short term nature of this study.

Pain scores

Pain was mainly reported in the included studies using a VAS score. The VAS is a psychometric response scale which is used in questionnaires, typically by getting patients to indicate on a pain scale (a 10 cm line) where their present sensation of pain lies. It is then measured, providing a numerical output between 1 (no pain) and 10 (most pain imaginable). Pain VAS scores can then be used to categorise people as responders and non-responders, such that a responder is a person who experiences sustained reduction of 50% or more of their pain sensation. This is a standard measurement of pain relief which has been extensively used in the medical literature, including TA 159 (Simpson *et al.*, 2008).

A comparison of VAS pain scores for leg and back pain reported in the studies is summarised in [Table 3.3](#). Note that for the SENZA-RCT study,

numerical data were only reported for baseline and 24 months post-procedure. Full longitudinal VAS data for back and leg pain is presented in Figure 8 of the submission. Similarly, data from the Al-Kaisy study (2016) is presented graphically in Figure 16 of the submission.

Table 3.3. *Back and Leg Pain VAS reported in the included studies.*

	Study	Intervention	VAS pain (cm) at various time points following permanent implantation (SD, where reported).					
			Baseline	Post-procedure	3 months	6 months	12 months	24 months
Back pain	SENZA-RCT*	Senza HF10	7.4 (1.3)	N/R	2.3†	2.2†	2.4†	2.4 (2.3)
		LF SCS	7.8 (1.2)	N/R	3.6†	3.8†	4.0†	4.5 (2.9)
		Comparison	Absolute difference at 24 months: -1.7 (95% CI: -2.6 to -0.8, p<0.001)					
	SENZA-EU	Senza HF10	8.4	N/R	2.4	2.7	2.8	3.3
	Russo (2016)**	Senza HF10	7.4	3.2	3.9	3.8	N/R	N/R
	Rapcan (2015)***	Senza HF10	8.7 (0.88)	3.9 (1.1)	4.4 (1.4)	4.4 (1.5)	4.0 (1.5)	N/R
Leg pain	SENZA-RCT*	Senza HF10	7.1 (1.5)	N/R	2.3†	2.8†	2.6†	2.4 (2.5)
		LF SCS	7.6 (1.4)	N/R	4.2†	4.1†	4.4†	3.9 (2.8)
		Comparison	Absolute difference at 24 months: -1.0 (95% CI: -2.0 to -0.8, p<0.003)					
	SENZA-EU	Senza HF10	5.4	N/R	1.3	1.4	2.0	2.3
	Russo (2016)**	Senza HF10	7.1	2.7	3.8	3.7	N/R	N/R
	Rapcan (2015)*** (SD)	Senza HF10	N/R	N/R	N/R	N/R	N/R	N/R
<p>Abbreviations. CI: confidence interval; LF: low frequency; N/R: not reported; NPRS: numerical pain rating score; SD: standard deviation; VAS: visual analogue scale.</p> <p>* Full longitudinal results of SENZA-RCT VAS pain outcomes presented as graph only (see Figure 8 of company's submission).</p> <p>** Employed NPRS system (gives pain rating of 1 to 10, similar to VAS).</p> <p>*** Reported combined pain for back and leg. Patients had predominant back pain.</p> <p>† Data estimated directly from graph (Figure 8 of company's submission)</p>								

The SENZA-RCT reported statistically significant improvements in leg and back VAS pain scores compared with baseline, and significant reductions compared with low frequency SCS at every follow up time point (post-implant, 3 months, 6 months, 12 months, and 24 months). Error bars reporting standard error of mean (SEM) were narrow, indicating there was a high degree of certainty around the point estimate. At 24 months follow up, there was a mean reduction of back pain VAS -1.7 (95% CI: -2.6 to -0.8, $p < 0.001$) compared with low frequency SCS. For leg pain, this was -1.0 (95% CI: -2.0 to -0.8, $p < 0.003$).

The results from the observational studies are largely consistent with those of the SENZA-RCT study (see [Table 3.3](#)). The SENZA-EU study (Van Buyten *et al.*, 2013; Al-Kaisy *et al.*, 2014) reported statistically significant improvements in both back and leg pain at all time points up to 2 years. Similar reductions in pain were reported in the Australian retrospective study (Russo *et al.*, 2016), the Slovakian study (Rapcan *et al.*, 2015), and the study by Al-Kaisy (2017), which was restricted to patients naïve to surgery.

The proportion of responders at 3 months was the primary outcome of the SENZA-RCT study (Kapural *et al.*, 2015). In patients receiving Senza SCS, 84.5% experienced a significant reduction in pain at 3 months, compared with 43.8% in the low frequency SCS group; this was a statistically superior result ($p < 0.001$). Similar findings were reported for other time points and also for the proportion of “remitters” (patients reporting back or leg pain VAS of 2.5 cm or less). These data are reported in Table 22 of the submission with accompanying graphs in Figure 7 and Figure 9 (which illustrates individual patient data).

Duration of pain relief

Duration of pain relief was not a specific outcome in any of the included studies. The SENZA-RCT reported significant improvements in pain at 24 months compared with baseline and low frequency SCS (Kapural *et al.*, 2016c). The SENZA-EU study reported similar findings at 24 months for Senza HF10 therapy compared with baseline (Al-Kaisy *et al.*, 2017). However, there was a possible trend 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.

Patient satisfaction

Questionnaires were used to assess patient satisfaction in the SENZA-RCT study (Kapural *et al.*, 2015; Kapural *et al.*, 2016c). At 12 months, significantly

more patients stated they were “very satisfied” with Senza HF10 therapy compared with low frequency SCS ($p = 0.01$). At 24 months, the majority of patients (60.0%) stated they were “very satisfied with Senza HF10 therapy compared with 40.4% of patients receiving low frequency SCS. This difference did not achieve statistical significance ($p = 0.07$). Most patients were satisfied with all aspects of charging the SCS devices, although there was no significant difference between Senza SCS and the Precision Plus (Boston Scientific) system (note: other low frequency SCS have different recharging schedules, or do not require recharging).

The single-armed studies also reported high levels of patient satisfaction with Senza HF10 therapy (Al-Kaisy *et al.*, 2017; Rapcan *et al.*, 2015), including the SENZA-EU study where 85% of patients were satisfied or very satisfied with treatment, and the same proportion would recommend it to others with similar pain conditions (Van Buyten *et al.*, 2013). In the short-term study by Tiede *et al.* (2013), 88% of patients expressed a preference for the Senza HF10 system compared with the low frequency SCS they had used immediately prior to this.

Health-related quality-of-life

Health-related quality of life (HRQoL) was not an outcome of the SENZA-RCT study, therefore comparative data on this is not available.

One small observational study in patients who were naïve to surgery reported on HRQoL using both the Euroqol-5D (EQ-5D) and short form-36 (SF-36) questionnaires (Al-Kaisy *et al.*, 2017). The authors reported “significant improvements in the self-reported scores at all timepoints” compared with baseline. These data are represented graphically in Figure 17 of the company’s submission.

Functional disability measures

Oswestry Disability Index

The principal functional disability score reported in the studies was the Oswestry Disability Index (ODI) (Fairbank, 1995). This is a self-reported questionnaire that measures functional disability in up to ten domains. Scores are averaged to give an overall aggregate score that is expressed as a percentage and interpreted such that patients are classified as having minimal disability ($\leq 20\%$), moderate disability (21 to 40%), severe disability (41 to 60%), crippled (61 to 80%) or bedbound or exaggerating symptoms (81 to 100%).

The SENZA-RCT reported comparative ODI between Senza HF10 and low frequency SCS arms. At 12 months, 62.9% of HF10 therapy subjects had

minimal or moderate disability compared with 45.7% of traditional SCS subjects ($p = 0.03$) (Kapural *et al.*, 2015). At 24 months, 23.5% of subjects receiving Senza HF10 therapy reported minimal disability compared with 9.9% of low frequency SCS participants (Kapural *et al.*, 2016c). Full results of ODI categorisation are reported in the respective papers.

The included observational studies all reported significant improvements in ODI associated with Senza HF10 therapy. The SENZA-EU study reported longitudinal ODI results (Van Buyten *et al.*, 2013; Al-Kaisy *et al.*, 2014). At baseline, the mean ODI score was 55%. This statistically significantly reduced to 37%, 38% and 40% at 3, 6, and 24 months respectively. The retrospective Australian study (Russo *et al.*, 2016) reported an initial mean score of 41.4% which immediately reduced to 31.5% post-procedure. This significant reduction was sustained at 3 months (34.4%) and 6 months (32.8%). Positive results were also observed in the small UK case series, with “average ODI scores were almost halved at the end of the study, and four previously *disabled or crippled* subjects reverting to the *minimally disabled* category” (Al-Kaisy *et al.*, 2017)

Other functional disability measures

The SENZA-RCT study reported that both Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) at 12 and 24 months were superior for Senza HF10 therapy compared with low frequency SCS ($p < 0.01$). There was a statistically significant improvement associated with Senza HF10 therapy compared with low frequency SCS. Using the Global Assessment of Functioning (GAF) at 12 months, 70.8% of subjects receiving Senza HF10 therapy had no symptoms to transient symptoms, compared with 59.3% of traditional low frequency SCS patients. This result trended towards, but did not achieve, significance ($p = 0.15$).

The study by Rapcan *et al.* (2015) reported significant improvements in “performance status” at 6 and 12 months compared with baseline. This outcome does not appear to be validated.

Other activities

Comparative data on sleeping and driving was not reported in the published papers of the SENZA-RCT study (Kapural *et al.*, 2015; Kapural *et al.*, 2016c), although in Table 23 of the submission it is reported that these were significantly improved with Senza HF10 compared with low frequency SCS (source unknown). The SENZA-EU study reported significant improvements in sleeping compared with baseline (Al-Kaisy *et al.*, 2014; Van Buyten *et al.*, 2013). Sleep quality was also reported to be improved in the small case series by Al-Kaisy *et al.* (2017).

Opioid and other analgesic use

Several of the included studies provided limited data on opioid and analgesic drug use.

The SENZA-RCT reported baseline and 12 month data on opioid use in both arms (Kapural *et al.*, 2015), but not data at 24 months (Kapural *et al.*, 2016c). The authors reported a statistically significant greater relative reduction in opioid use in the Senza HF10 therapy arm compared with the low frequency SCS arm.

The SENZA-EU study reported 86% of patients were receiving opioid analgesia at baseline. This decreased to 57% at 24 months ($p < 0.001$) (Al-Kaisy *et al.*, 2017). The Slovakian study reported 65% of patients had their opioid consumption reduced by a half or more at 12 months compared with baseline (Rapcan *et al.*, 2015). The study by Al-Kaisy (2017) reported patients reduced their daily opioid dose from 112 (± 87 SD) to 40 (± 13 SD) morphine milligrams equivalent (relative reduction 64% $p = 0.083$) at 12 months.

Device-related adverse events

Device-related adverse events were described in each study, but with inconsistent definitions used across the published papers. These are summarised in detail in section 3.7 of this report.

Incidence of paraesthesia

The SENZA-RCT study reported no subjects receiving Senza HF10 therapy experienced induced paraesthesia or stimulation-related discomfort. This compared with 46.5% of low frequency SCS subjects who reported uncomfortable stimulation.

The proof of concept study noted “high-frequency investigational stimulation parameters did not produce a paraesthesia” (Tiede *et al.*, 2013).

Implant lifetime

Implant lifetime was not an outcome reported by the included studies. The expected lifetime of the Senza implant is 10 years (Nevro Corp, 2015) whereas the maximum study follow up time was 2 years for the SENZA-RCT and SENZA-EU studies. The lifetime of low frequency SCS devices varies, and is dependent on whether the technology incorporates a rechargeable battery or not.

Reason for implant removal

The company reported unpublished data from the SENZA-RCT trial (academic in confidence) of the number of explanted Senza and low frequency SCS devices, and the reasons for explantation (Table 24 of the submission). After 2 years, [REDACTED] of patients who received Senza retained the implanted device.

[REDACTED]
[REDACTED]
[REDACTED] In comparison, [REDACTED] of the patients who received low frequency SCS retained the device.

[REDACTED]
[REDACTED]

3.6.3 Summary of results

The EAC has summarised the results of the included studies according to the outcomes reported in the decision problem in [Table 3.4](#). The EAC considered that the results from the SENZA-RCT, supported by data from the single-armed studies, provided unequivocal evidence that the use of Senza HF10 therapy is associated with a large and sustained reduction in back and leg pain in the indicated population. Furthermore, the reduction in pain was significantly greater than observed for standard low frequency SCS. The magnitude of the pain reduction compared with baseline and low frequency SCS is likely to be clinically important.

The reduction in pain reported with Senza HF10 therapy would be expected to have positive patient benefits. This is largely reflected by the secondary outcomes, which indicate Senza HF10 therapy results in significant improvements including a reduction in disability and increase in quality of life. The EAC also accepts that, unlike traditional low frequency SCS, Senza HF10 does not cause paraesthesia, which is poorly tolerated by some patients. An additional benefit is that Senza HF10 is not affected by postural changes, which allows the patient to drive and operate machinery whilst the device is active.

The EAC's opinion on how the claimed benefits of the device, listed in the scope (NICE, 2017c), are substantiated are listed in [Table 3.5](#).

Table 3.4. Summary of level of evidence for outcomes reported in the scope of the decision problem.

Outcome (as described in decision problem)	Comparative evidence of Senza HF10 with low frequency SCS. Evidence from SENZA-RCT (Kapural <i>et al.</i> , 2015; Kapural <i>et al.</i> , 2016c).	Non-comparative evidence: changes from baseline associated with Senza HF10. Evidence from SENZA-RCT and single-armed studies (citations stated).	EAC comment
Pain scores	<p>Strong evidence of superiority in reduction of VAS pain scores for back and leg pain.</p> <p>Strong evidence of greater number of responders for back and leg pain. 85% vs 44% response at 3 months (primary outcome).</p>	<p>Strong evidence of improvements in back and leg pain [refs]. Treatment reduces back and leg pain by approximately 50%.</p> <p>(Al-Kaisy <i>et al.</i>, 2014; Van Buyten <i>et al.</i>, 2013)</p> <p>(Russo <i>et al.</i>, 2016)</p> <p>(Rapcan <i>et al.</i>, 2015)</p> <p>(Al-Kaisy <i>et al.</i>, 2017)</p>	<p>There is unequivocal evidence that Senza HF10 is associated with reduced back and leg pain compared with baseline and low frequency SCS.</p> <p>Size of placebo effect unknown.</p>
Duration of pain relief	<p>Pain relief observed for minimum of 24 months.</p>	<p>Pain relief observed for minimum of 24 months (Al-Kaisy <i>et al.</i>, 2014).</p>	<p>Battery life of implant is 10 years. However, clinical effectiveness cannot be extrapolated beyond 2 years with 100% confidence.</p>

Outcome (as described in decision problem)	Comparative evidence of Senza HF10 with low frequency SCS. Evidence from SENZA-RCT (Kapural <i>et al.</i>, 2015; Kapural <i>et al.</i>, 2016c).	Non-comparative evidence: changes from baseline associated with Senza HF10. Evidence from SENZA-RCT and single-armed studies (citations stated).	EAC comment
Patient satisfaction	Strong evidence patient satisfaction is greater for Senza HF10 therapy at 12 months.	Strong evidence of patient satisfaction (Al-Kaisy <i>et al.</i> , 2017; Rapcan <i>et al.</i> , 2015; Tiede <i>et al.</i> , 2013).	Patient satisfaction with both technologies is high. However, there is a preference for Senza HF10 where the option is given.
Health-related quality-of life	No comparative evidence, Generic HRQoL was not an outcome of the SENZA-RCT study.	Evidence of improved HRQoL at time points up to 12 months (Al-Kaisy <i>et al.</i> , 2017).	Evidence of HRQoL improvement restricted to patients naïve to back surgery. However, given observed functional and wellbeing improvements, improved HRQoL is highly plausible.
Functional disability measures	Strong evidence of superiority using ODI, CGIC, and PGIC measurements.	Strong evidence of improvements in ODI (Al-Kaisy <i>et al.</i> , 2017; Al-Kaisy <i>et al.</i> , 2014; Russo <i>et al.</i> , 2016; Van Buyten <i>et al.</i> , 2013). Evidence of improved sleep functioning (Al-Kaisy <i>et al.</i> , 2017; Al-Kaisy <i>et al.</i> ,	As well as improvements in physical and mental functioning, Senza HF10 preserves ability to drive, and improves sleep quality.

Outcome (as described in decision problem)	Comparative evidence of Senza HF10 with low frequency SCS. Evidence from SENZA-RCT (Kapural <i>et al.</i> , 2015; Kapural <i>et al.</i> , 2016c).	Non-comparative evidence: changes from baseline associated with Senza HF10. Evidence from SENZA-RCT and single-armed studies (citations stated).	EAC comment
		2014; Van Buyten <i>et al.</i> , 2013).	
Opioid and other analgesic use.	Weak evidence of reduced opioid use.	Evidence of reduction in use of opioid analgesia (Al-Kaisy <i>et al.</i> , 2017; Al-Kaisy <i>et al.</i> , 2014; Rapcan <i>et al.</i> , 2015).	Reduction of opioid use is plausible and consistent with reduced pain perception.
Device related adverse events	Strong evidence Senza HF10 has fewer adverse events than low frequency SCS.	Consistent observational evidence of adverse event rates ranging from 19 to 46% at 12 months (Al-Kaisy <i>et al.</i> , 2014; Van Buyten <i>et al.</i> , 2013), (Al-Kaisy <i>et al.</i> , 2017), (Rapcan <i>et al.</i> , 2015)	Device related adverse events for Senza SCS are broadly comparable with those found for low frequency SCS in NICE TA 159
Incidence of paraesthesia.	Strong evidence Senza HF10 does not cause paraesthesia.	Strong evidence Senza HF10 does not cause paraesthesia (Tiede <i>et al.</i> , 2013).	Senza HF10 does not cause paraesthesia. Low frequency SCS may cause unpleasant or intolerable paraesthesia in a proportion of patients.

Outcome (as described in decision problem)	Comparative evidence of Senza HF10 with low frequency SCS. Evidence from SENZA-RCT (Kapural <i>et al.</i> , 2015; Kapural <i>et al.</i> , 2016c).	Non-comparative evidence: changes from baseline associated with Senza HF10. Evidence from SENZA-RCT and single-armed studies (citations stated).	EAC comment
Implant lifetime	No evidence.	No evidence.	Implant lifetime estimated at 10 years before replacement necessary (Nevro Corp, 2015).
Reasons for implant removal	<u>Unpublished evidence does not indicate significant differences between technologies.</u>	No evidence.	<u>Reason for explantation was because of paraesthesia in two patients receiving low frequent SCS.</u>
<p>Abbreviations. CGIC: Clinician Global Impression of Change; HRQoL: Health related quality of life; ODI: Oswestry Disability Index; PGIC: Patient Global Impression of Change</p>			

Table 3.5. *Substantiation of claimed patient benefits.*

Claimed patient benefit (compared with low frequency SCS)	Substantiated? (Fully, partially or not)	EAC comment
Clinically superior pain relief (almost twice as much when measured using a VAS score) for the majority of patients with predominant back pain, as well as those with predominant leg pain.	Fully	Principal evidence from Senza-RCT supported by observational studies.
Increased achievement of a successful outcome (greater than or equal to a 50% reduction in pain) compared with low frequency SCS.	Fully	Evidence from Senza-RCT.
A significantly better functional outcome.	Fully	Substantiated by comparison of ODI scores and distribution.
The delivery of treatment without paraesthesia can therefore be continued during sleep and while driving or operating machinery.	Partially	Senza HF10 does not cause paraesthesia and driving is not contraindicated. Comparative sleep data not reported in published records of Senza-RCT.
Sustained and long term improvement in pain relief and function (RCT follow-up data currently to 24 months).	Fully	Comparative data supports efficacy up to 24 months.
May reduce the need for concomitant pain medication and potentially follow-up attendance at pain clinics.	Partially	Comparative evidence of opioid use (at 12 months) not conclusive. No data on follow up for pain clinics.
Abbreviation: ODI: Oswestry Disability Index.		

3.7 Description of the adverse events

Adverse events were inconsistently defined across the included studies. The EAC has therefore summarised those described as 'serious' adverse events, versus 'adverse events' in [Table 3.6](#), for clarity. It can be seen that a number of events are considered serious by some authors and not by others (**in bold font** in [Table 3.6](#)). It is therefore important to consider that reported overall adverse event rates in the literature for SCS should be scrutinised for their constituent descriptors and interpreted with caution.

[Table 3.6](#) may be compared with the definitions of adverse events used in NICE TA 159 for consistency. Rather than defining events as 'serious' or not, TA 159 considered whether adverse events could be attributed as SCS device-related, or non-SCS device-related. SCS device-related complications included electrode migration, lead fracture, loss of paraesthesia, dural puncture and infection. Non-SCS device-related events included drug adverse events, extra pain events, new illness/injury/condition and worsening pre-existing conditions (Simpson *et al.*, 2008).

Table 3.6. Adverse event definitions used in the included studies.

Serious Adverse Event definitions (SAEs)	Adverse Event definitions (AEs)
Wound complications ¹	Implant site pain ^{1,2} (with and without surgical revision) ⁶
Arrhythmia ¹	Uncomfortable paraesthesias ^{1,2}
Cardiac arrest ¹	Lead migration^{4,6,7} (with and without surgical revision)^{1,2}
Extradural abscess ¹	Undesirable sensation (resolved with reprogramming / without re-intervention) ⁵
Intracranial hypotension ¹	Muscle cramps / spasms ⁴ (resolved with reprogramming / without re-intervention) ⁵
Paresis ¹	Pocket / anchor site pain^{4,6,7}
Post-lumbar puncture syndrome ¹	Wound infection^{4,7}
Pocket pain^{3,4}	Hematoma / seroma / implant site oedema ⁴
Wound infection^{3,4}	Temporary nerve irritation ⁴
Lead migration^{3,4}	Skin irritation ⁴
Loss of therapy effect^{3,4}	Loss of therapy effect^{4,7,8}
Sub-optimal lead placement^{3,4}	Sub-optimal lead placement⁴
Skin erosion ³	Thrombosis ⁴
Death ²	Other/Unknown ^{4,7}
1. Kapural 2016a (SENZA RCT – 24 month data) 2. Kapural 2015 (SENZA RCT – 12 month data) 3. Al-Kaisy 2014 (SENZA EU – 24 month data) 4. Van Buyten 2013 (SENZA EU – 12 month data) 5. Tiede 2013 6. Al-Kaisy 2016b 7. Russo 2016 (The listed outcomes are described in this study as ‘Reasons for lack of significant pain relief’, rather than adverse events) 8. Rapcan 2013 (A loss of therapy effect was described in this study as a “special” subgroup, rather than adverse event)	

The company tabulated details in section 7.7.2 of their submission of 'all important adverse events reported for each study'. The EAC independently checked all tabulated data in the company's submission against the original published papers and identified some omissions, briefly described below.

The summary list of reported 'serious' adverse events (SAEs) in Table 38 of the company's submission (from the Senza arm of the SENZA-RCT by Kapural *et al.* 2016) is: wound complications 4.0% (n = 4/101) and paresis 1.0% (n = 1/101). Additional SAEs reported for traditional low frequency SCS in the comparator arm include: arrhythmia, cardiac arrest, extradural abscess, intracranial hypotension, and post-lumbar puncture syndrome (total comparator SAE rate 7.2%). However, there were a number of additional adverse events in the SENZA-RCT that have been omitted by the company in their submission. These are tabulated by the EAC above ([Table 3.6](#)) and calculated as an overall rate of patients with one or more adverse event of 31.7% in the Senza HF10 arm and 40.2% in the low frequency SCS arm (using the ITT cohort in the denominator, [Table 3.7](#), below).

The summary list of reported serious adverse events (SAEs) in Table 39 of the company's submission (from 24 month data in the SENZA-EU study by Al-Kaisy *et al.* (2014) is: pocket pain, wound infection, lead migration, loss of therapy effect, sub-optimal lead placement and skin erosion (total rate = 24.0%). The company omitted to summarise the 12 month data published by Van Buyten *et al.* (2013), which describes 51 events in 38/83 patients (46.0%), of which 25% (13/51) were defined as 'serious' events, in the trial plus implant cohort.

The summary list of reported adverse events (AEs) in Table 40 of the company's submission (from the study by Tiede *et al.* 2013) is: undesirable sensation and muscle cramps / spasms (total rate = 12.0%). The EAC did not identify any additional adverse events reported by these authors.

The company correctly summarised the description of all adverse events reported by Al-Kaisy *et al.* (2016b), which the EAC calculated as a rate of 23.8% (5/21) ([Table 3.7](#)).

The company's submission stated that no adverse events were reported in the remaining studies, which the EAC found to be inaccurate. Although not described in terms of adverse events, both Russo *et al.* (2016) and Rapcan *et al.* (2015) described events which were considered adverse by other authors (summarised by the EAC in [Table 3.7](#), below).

Table 3.7. EAC calculations of overall rates of any adverse event, as reported in the included studies.

Study	Intervention	Timeline	Patients with ≥ 1 adverse event (n)	EAC comment
SENZA-RCT	Senza HF10	12 months	31.7% (32/101)	The authors report the ITT cohort as denominator of adverse and serious adverse event rates. This therefore includes patients who were never implanted.
	LF SCS	12 months	40.2% (39/97)	
SENZA-EU	Senza HF10	12 months	46.0% (38/83)	51 events in 38 patients, 25% (13/51) of which were defined as 'serious' events, in the trial + implant cohort.
	Senza HF10	24 months	24.1% (20/83)	Defined as 'serious' events in the trial + implant cohort.
Tiede (2013)	Senza HF10	4 days	12.0% (3/25)	A total of 3 adverse events during the investigational trial phase.
Al-Kaisy (2016b)	Senza HF10	12 months	23.8% (5/21)	Rate calculated in the trial + implant cohort.
Russo (2016)	Senza HF10	6 months	Not reported	Although numbers of patients with ≥ 1 adverse event were not defined as such, there were 3 instances of lead migration, 2 of pocket / anchor site pain, 1 of infection and 1 loss of therapy efficacy. These were reported as 'Reason for lack of significant pain relief'.
Rapcan (2015)	Senza HF10	12 months	19% (4/21)	Although adverse events were not defined as such, a loss of therapy effect was described in this study as a "special" subgroup, rather than adverse event. These patients had to switch between high frequency SCS and a traditional SCS program every 4 to 5 weeks.

The company reported in section 7.7.3 of their submission that no UK Medicines and Healthcare products Regulatory Agency (MHRA) field safety notices or device alerts were identified at the time of writing (13/01/2017). The company identified 15 US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) medical device reports in the period 12/01/2016 to 31/12/2016. The majority of these were reported as infections, which were treated with intravenous antibiotics, resulting in no further reported complications. 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.

The EAC independently searched for the 'Senza' Brand Name and 'Nevro' Manufacturer on the FDA MAUDE website (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm>) on 27/06/2017, without applying any date limits, and extracted 271 resultant records. The event dates ranged from 20/08/2015 to 05/05/2017. A review of these by the EAC showed that they were categorised by Event Type as: 'Injury' (n = 252), 'Malfunction' (n = 13) and 'Death' (n = 6). The Manufacturer Narrative in each record indicates that all reports to the FDA were appropriately investigated by the company in a timely fashion. None of the deaths were found to be attributable to the device. It is important to note that the FDA states that their medical device report data alone "cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices."

A confirmatory search of the UK MHRA alerts and recalls for drugs and medical devices (<https://www.gov.uk/drug-device-alerts>) by the EAC on 26/06/2017 found no records for either the 'Senza' device, or 'Nevro' company name.

The EAC concludes that the Senza device appears to have a similar safety profile to traditional low frequency SCS devices and comparable with the adverse event rates found in NICE TA 159 of 5 to 38% of implantations requiring surgery to resolve a device-related complication, including device removals (Simpson *et al.*, 2008). One advantage of Senza is that the adverse event of uncomfortable paraesthesia, reported in 11.3% of patients in the SENZA-RCT for the comparator arm, is omitted when using HF10 therapy.

The adverse events reported by the company therefore do not raise any new safety concerns for the Senza technology being evaluated.

3.8 Planned and on-going studies

The company identified two on-going studies in Section 5.1 (Table 4) of the submission. It is not clear how these studies were identified by the company, although it is likely both were sponsored by Nevro Corp. One of the studies, set in Australia, has been independently identified by the EAC, whereas the other study, set in Belgium, was not identified ([Appendix C](#)). An additional study was identified by the company from a focussed search of ClinicalTrials.gov. This study, a single armed observational study set in Leeds (UK) (NCT02689375, 2015) was identified by the EAC's repeat of the company's literature search ([Section 3.1](#)).

The EAC replication of the company's literature search strategy had excluded a number of trial protocols at first sift. These were checked for any additional relevant on-going studies. Four in scope were identified in the ISRCTN registry (International Standard Randomised Controlled Trial Number, www.isrctn.com) and a further two were identified in the clinicaltrials.gov website (both for chronic pain in the upper limbs / neck). The company stated in Section 5.1 of the submission that both of these trials registries had been searched for the terms "Nevro", "Senza", "high frequency" and "spinal cord stimulation", but these six records were omitted from the submission. The EAC has summarised these six studies in [Appendix C](#).

The EAC identified an additional 60 potential study protocols through its additional literature search. Of these, 57 were identified as not relevant from the abstract alone. Three were identified as potentially relevant and the records retrieved. These are listed in [Appendix C](#). In addition to this, the EAC also identified another study of interest (the PROVA study), during its rerun of the company's literature search which appears to have been prematurely terminated; this is also listed in [Appendix C](#).

Thus in total, twelve on-going or terminated studies were identified by the company and/or the EAC. The majority of these studies were single-armed observational studies or registries (ACTRN12614000665639, 2014b; ISRCTN11720855, 2017; ISRCTN13607429, 2016; ISRCTN13674719, 2017; ISRCTN54708653, 2016; NCT02385201, 2015; NCT02689375, 2015; NTR4965, 2014). However, protocols for two sham-controlled crossover RCTs were also identified. One of these studies was a non-company sponsored study set in Australia and is not recruiting yet (ACTRN12614000236695, 2014a). The other study was sponsored by Nevro Corp, but has been terminated before results were available for publication (van Buyten *et al.*, 2011). The EAC clarified the reasons for the study's early termination with the company. The company said that practical difficulties had

arisen because devices took longer to charge if activated, thus patients deduced whether they were in the intervention or control arm (i.e. unmasking occurred) (NYEAC, 2017).

The EAC also identified a conference abstract of another sham-controlled trial published in the UK (Al-Kaisy and Palmisani, 2016) from a review of the mechanism of high frequency SCS (Linderoth and Foreman, 2017). This experimental study, which has not been published or peer reviewed, reported sub-perceptible stimulation of the spinal cord at frequencies of 1200Hz, at 3030Hz and at 5882Hz had a significant effect on pain reduction, with the higher frequency demonstrating the greatest effect. However, sham stimulation was also associated with a significant reduction in pain compared with baseline.

Pain reduction with sham high frequency SCS has been reported previously in the literature. In 2012, Perruchoud *et al.* performed a cross over trial where 33 patients were randomised to receive high frequency SCS (5 kHz) or sham following traditional low frequency SCS (Perruchoud *et al.*, 2013). After a washout period with traditional SCS, patients were crossed over to the alternative treatment. Because the patients cannot feel SCS at this frequency and masking was effectively maintained, the patients were unaware of the order of their treatment allocations. The authors reported there was a highly significant “period” effect regarding the time of treatment, but that high frequency SCS at 5 Hz was not statistically significantly superior to placebo. Limitations of this study were that the period of treatment duration and washout were short, meaning it is difficult to extrapolate the effect into real-life clinical practice. This study used a different device from another manufacturer, which utilised a different frequency, pulse width, and amplitude, compared with Senza HF10 technology.

4 Economic evidence

4.1 Published economic evidence

4.1.1 Critique and rerunning of the company's search strategy

Sections 8.1.1 and 10.3 (Appendix 3) of the company's submission report the search methodology used to identify economic evidence. The search methods reported in the submission do not contain sufficient detail to be certain of the exact search methods used, but enough information was provided for the EAC to make an informed judgement as to how the searches were conducted, and the company's searches were re-run on this basis. The re-run company's searches retrieved 18 records. After de-duplication, 16 records remained.

The company's search methods had some limitations which could potentially impact on search sensitivity. A full critique of the company's search methods is provided in [Appendix A5](#). A description of the methods used in the re-running of the company's searches is provided in [Appendix A6](#). The searches carried out by the EAC to identify clinical effectiveness evidence (reported in [Section 3.1](#) and [Appendix A3](#)) were not restricted by study design and were prospectively designed to retrieve both clinical effectiveness and economic evidence. No additional *de novo* EAC literature search for economic evidence was therefore required.

4.1.2 Critique of the company's study selection

The inclusion and exclusion criteria used by the company were reported in Table 41. The searches were limited to publications from 2006 to present (at December 2016), reflecting the timeframe of the existence of the company (Nevro Corp.) Studies were included if they included outcomes on costs, incremental costs, quality adjusted life years (QALY), budget impact, or incremental cost effectiveness ratios (ICERs). The EAC considered that these eligibility criteria were appropriate.

The company reported the selection of studies in PRISMA format in Figure 27. Reasons for exclusion were described at each stage of the sift. From the initial identification of 47 potentially relevant studies, 17 were retrieved in full format for review. Of these, 16 were excluded for being on the wrong intervention (n = 2), the wrong outcomes (n = 10), or were reviews or editorials (n = 4). This left one study for inclusion. Further details on the reasons for exclusion were not supplied.

The EAC identified 16 potentially relevant studies for review. Of these, 15 were excluded, mainly for being out of scope (n = 9), or being reviews or guidelines (n = 6). This left one study for inclusion.

4.1.3 Included and excluded studies

Through their literature searches and sifts, the company and EAC each identified one economic study as being within scope and relevant for full appraisal.

As both the EAC and the company independently identified this study and excluded all others, the EAC was satisfied that the sifting process had been conducted appropriately.

4.1.4 Overview of methodologies of all included economic studies

The included study was a cost-effectiveness study comparing the use of Senza HF10 therapy with CMM, reoperation, and traditional rechargeable and non-rechargeable low frequency SCS technology (Annemans *et al.*, 2014). The study reported results from a health economic model of SCS which had a UK NHS perspective, a 15 year time horizon, and compared HF10 therapy with CMM, reoperation, and traditional rechargeable and non-rechargeable low frequency SCS technology. Results were expressed as ICERs.

The study reproduced the original decision analytic model structure that was used to inform NICE TA 159 (Simpson *et al.*, 2008). This comprised both a decision tree and a Markov model. As the study was undertaken before the publication of the SENZA-RCT study, clinical effectiveness parameters modelled for the Senza HF10 intervention were informed by the SENZA-EU observational study (Van Buyten *et al.*, 2013).

The structure of the model and its inputs (Annemans *et al.*, 2014) formed the basis of the company's *de novo* model (see [Section 4.2](#)).

4.1.5. Overview and critique of the company's critical appraisal for each study

The company critically appraised the Annemans study using the Drummond checklist for appraisal of economic studies (Drummond *et al.*, 2005) in Table 43 of the submission. This was considered appropriate by the EAC. As the EAC agreed with this appraisal, it has not been formally repeated. The EAC concurs with the company's statement that the study was "judged to be of high quality".

4.1.6 Does the company's review of economic evidence draw conclusions from the data available?

The company summarised the results of the study by Annemans in Table 42 of the submission (Section 8.2.1). From a simulated cohort of 1,000 patients, Senza HF10 therapy was found to be the most cost-effective option of the interventions analysed. The ICER was £3,153 and £2,666 compared with CMM and reoperation respectively. Senza HF10 dominated both rechargeable and non-rechargeable low frequency SCS technologies; that is, it was more effective and less expensive.

The cost saving potential of Senza HF10 technology was investigated in detail by the *de novo* model ([Section 4.2](#)).

4.2 Company *de novo* cost analysis

The company provided a *de novo* cost analysis in Section 9 of the submission and a description of the model in Section 9.1. The EAC describes the rationale for this particular model in [Section 4.2.1](#). The EAC agrees with the company on the suitability of the model and the rationale for its development. The following sections briefly describe the background to the model, the scope of the model using PICO analysis (population, intervention, comparator, outcomes), and the model structure.

4.2.1 Background

As described in Section 9.1.1 of the company's submission, the model is an iteration of the model previously developed to inform TA 159 (NICE, 2008). This model was originally developed by the School of Health and Related Research (SchARR) at the University of Sheffield, who were the independent academic centre which produced the assessment report for this technology appraisal (Simpson *et al.*, 2008). The decision analytic model reported in the TA 159 assessment report was subsequently published with minor alterations in a later paper (Taylor *et al.*, 2010), and the removal of any implantation procedural costs, leaving device-only pricing. The focus of this study was the analysis of the impact on cost effectiveness of non-rechargeable versus rechargeable low frequency SCS implanted pulse generators.

In 2014, a model investigating the cost-effectiveness of Senza HF10 therapy compared with low frequency SCS was published (Annemans *et al.*, 2014). This was an iteration of the previously published models, using data from the SENZA-EU observational study (Al-Kaisy *et al.*, 2014, Van Buyten *et al.*, 2013), but not the comparative SENZA-RCT study (Kapural *et al.*, 2015, Kapural *et al.*, 2016). The company identified and critically appraised this study in their submission (see [Section 4.1](#)). The *de novo* model described in the company's submission is essentially a further development of the

Annemans study (2014), with the main change being to use clinical data from the SENZA-RCT study. It was developed by MTEch Access (<http://www.mtechaccess.co.uk>).

TA 159 and subsequent developments of the model used cost utility analysis which report incremental costs and utilities (derived from HRQoL) and are required for the development of NICE technical appraisals. However, MTEP has adopted a cost consequence analysis framework, requiring “a comparative evaluation of the costs and resource use consequences of two or more interventions considered alongside the relevant clinical benefits” (NICE, 2011). The company has addressed this throughout the report by omitting model outputs based on utilities in key results sections. Thus, although cost utility analysis has been performed, the EAC does not report these in this assessment report.

4.2.2 PICO analysis

Population

The company described the population used in the economic model as “Adult patients (≥ 18 years) experiencing chronic pain despite CMM in line with NICE TA 159 as outlined in the final scope”. This is the appropriate population and closely represents participants enrolled into the SENZA-RCT trial, which informed the clinical effectiveness parameters (Kapural *et al.*, 2015). However, results from this economic model should not be extrapolated to patients with neuropathic pain of the head, neck, arm, or patients with complex regional pain syndrome (CPRS) (see [Section 2.2](#)).

Although death was reported as an outcome in the model, a constant mortality rate was assumed across the cohorts, and there was no differential relating to age between intervention groups.

Intervention

The intervention was treatment using Senza HF10 with additional CMM as required. This was consistent with the scope (NICE, 2017c) and the clinical data (Kapural *et al.*, 2015).

Comparator

The comparator selected slightly deviated from the scope, which was “low frequency spinal cord stimulation (up to 1200 Hz)” (NICE, 2017c). For the economic model, the company selected two comparators; these were non-rechargeable and rechargeable low frequency SCS. The only differences between rechargeable and non-rechargeable SCS technologies were device longevity.

Outcomes

Outcomes used in the model were in line with published and unpublished data concerning Senza HF10 and its comparator from the SENZA-RCT trial (Precision Plus System; Boston Scientific). Clinical data informed transitional probabilities and cost data were applied to individual clinical states (see [Section 4.2.6](#)). The final calculated outcomes for cost consequence models are reported as cumulative and incremental costs.

Summary

A summary of the PICO analysis of the economic model is reported in [Table 4.1](#).

Table 4.1. *Summary of scope of de novo economic model.*

	Company's economic model	EAC comment
Population	Population described in TA 159 (patients eligible for low frequency SCS).	Population is appropriate and consistent with generalisable evidence from clinical data.
Intervention	Senza HF10 therapy.	Intervention is appropriate. No extrapolation required.
Comparator	Non-rechargeable low frequency SCS. Rechargeable low frequency SCS.	Two comparators to reflect main technical variation in devices. Comparator is appropriate.
Outcomes	Endpoint outcomes are costs.	Costs are the appropriate outcome for cost consequence models.

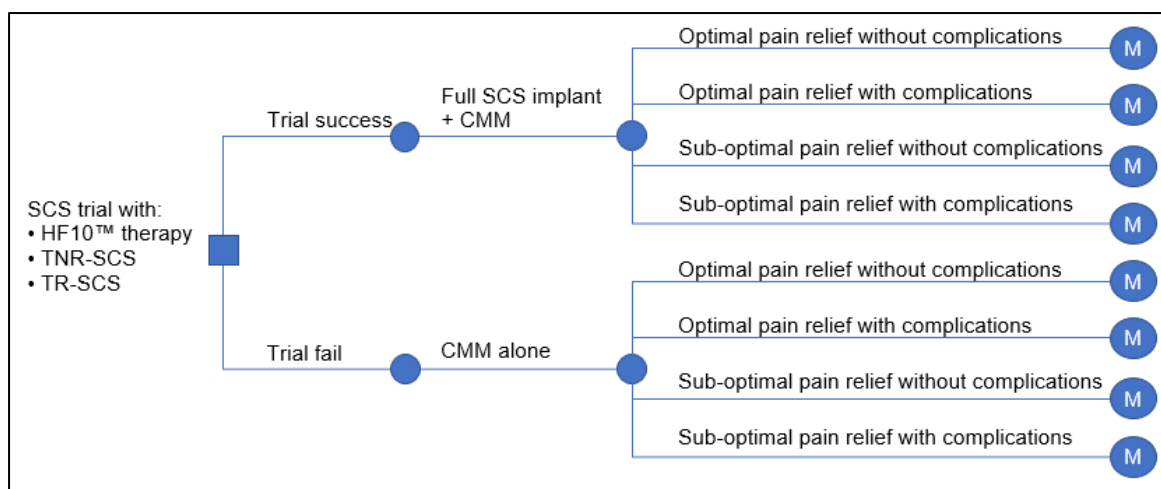
4.2.3 Model structure

The model structure is described fully in Section 9.1.4 of the company's submission and key aspects were independently assessed and are reported briefly by the EAC in the following section. The model, originally described in the TA 159 assessment report (Simpson *et al.*, 2008) is a two stage decision analytic model that utilises a decision tree for the initial 6 months, followed by a Markov state transition model with a time horizon of 15 years.

The decision tree stage is illustrated in [Figure 4.1](#) (also Figure 28 of submission). There is one model structure which is used to estimate patient flows and costs for a cohort of patients electing to have SCS (any type), of which some end up with CMM (alone). The model was run three times, with

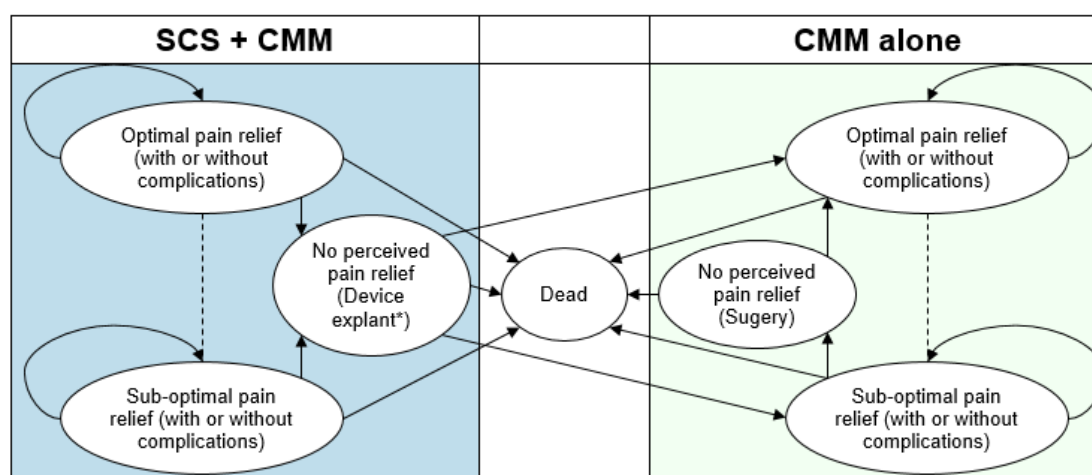
different parameters, to estimate lifetime costs for each of the three different types of SCS (Senza HF10 therapy, rechargeable low frequency SCS, non-rechargeable low frequency SCS). All interventions require an initial trial of treatment that can be successful or unsuccessful; patients that are successfully treated proceed to have a permanent implant of that intervention type. Patients in whom the trial was not successful continue on CMM; patients cannot receive any form of SCS treatment once they enter the CMM branch of the model. Patients receiving either CMM or SCS (any type) may receive optimal or suboptimal pain relief, and additionally may suffer complications (see below).

Figure 4.1. Schematic patient flow from de novo economic model.



The decision tree informs on costs up to 6 months and sets the initial cohort proportions for the subsequent Markov model (see [Figure 4.2](#), also Figure 29 of submission). Patients receiving SCS (any type) can experience optimal or suboptimal pain relief. The level of pain relief a patient experiences has a direct effect on the level of CMM they receive, and thus affects the cost of being in that clinical state (see [Section 4.2.7](#)). The model does not allow transition from optimal to suboptimal pain relief in either direction. In addition to level of pain relief provided, a proportion of patients in all clinical states at 6 months can experience “non-serious” complications of treatment that have a monetary impact on that cycle.

Figure 4.2. Markov model used in de novo economic model.



During each cycle, patients receiving SCS may experience no effect from the treating technology. Should this occur, the device is explanted and they move to the CMM part (arm) of the model. The proportion of patients entering the CMM side after an explant, who also have a complication, is not stated explicitly and is assumed to be the same as the long-term complication rate. Patients receiving suboptimal pain relief with CMM alone may receive repeat spinal surgery which will optimally improve pain symptoms. In the CMM arm of the model, multiple surgeries are possible in a single patient. In the SCS + CMM arm, multiple device explants are not allowed. The state “No perceived pain relief (Surgery)” also appears to be a Markov transition state. Again, the proportion of those having a complication after further surgery is not stated.

The EAC considers that the handling of complications in the model structure was not transparently reported in the original publication (Simpson *et al.*, 2008); but this aspect of the model has since been clarified with the company. In the short-term model, approximately [REDACTED] of patients suffer a complication and there are separate proportions for those having, for example, optimal pain relief with and without complications. In the long-term Markov model, a proportion of patients in the optimal and sub-optimal states are assumed to experience an AE in each cycle (independent of their previous states), at the rate specified (see [section 4.2.6](#)). These patients are then considered separately with regards to costs. This simplified approach to long-term complications was undertaken due to a lack of data to inform transitional parameters between states in the Markov model, and because the increased complexity would not materially alter the deterministic results.

All patients have an equal risk of dying in the Markov model. This risk is not related to use of a particular device, CMM or procedural or surgical risks. Therefore death does not influence the incremental results.

Model mechanics

The company's model was constructed using Microsoft Excel. The workbook consisted of 26 worksheets and incorporated Visual Basic macros for probabilistic sensitivity analysis, using a Monte Carlo approach (Sonnenberg and Beck, 1993). A brief description of the worksheets is reported in [Appendix D](#), Table D1.

In general, a Markov model with n states requires $n-1$ prevalences (starting proportions) to be defined. If "with complications" are defined as separate states, there are 11 states. The short-term model sets 8 starting proportions and the remaining three (dead, explant and surgery) are implicitly zero, so the EAC considers that the starting position is fully defined. A Markov model with n states has $n(n-1)$ transition probabilities (i.e. 110 in total for $n = 11$). Many are zero (i.e. no arrow in [Figure 4.2](#)) and all leading to "Dead" have the same value. Many of the remainder are defined in the company's submission and executable model, but it is not possible to establish which values have been used for all transitions from the company's narrative and annotated cells in the Excel spreadsheet alone, without making assumptions or reading the underlying code. It would have been preferable for the company to provide these in a matrix format with their submission.

4.2.4 Summary of company's base case results

The company's base case results were reported in Table 53 of the company's submission. The EAC has cross-referenced results reported in the document with the deterministic analysis of the model and summarised these in [Table 4.2](#).

Table 4.2. *Base case results of company's economic analysis.*

	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 non-rechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation.

As can be seen, in the base case analysis the use of Senza HF10 treatment is least costly over a 15 year time period. In comparison, rechargeable SCS is associated with an additional cost of £4,795 (about 5% of total costs), whereas non-rechargeable SCS is associated with an additional cost of £7,755 (about 8% of total costs). The unadjusted annual savings associated

with Senza HF10 therapy are relatively modest, at £320 and £517 compared with non-rechargeable SCS and rechargeable SCS respectively.

Further discussion of the results and their context is reported in [Section 4.4](#).

4.2.5 Model assumptions

The company listed the assumptions used in the model in Table 44 of the submission with accompanying justifications. The EAC has commented on these assumptions in [Appendix D](#) (Table D2). Most of the assumptions and parameters used were derived from TA 159, which has been previously validated (Simpson *et al.*, 2008), peer reviewed and published (NICE, 2008; Taylor *et al.*, 2010). The EAC considered that, although there was some lack of transparency concerning some aspects of the model structure and transition parameters (see [Section 4.2.6](#)), the company had tended towards conservative assumptions, which was appropriate. Additionally, uncertainties have been addressed through deterministic and probabilistic sensitivity analysis (see [Section 4.4.2](#) to [4.4.7](#)).

The health states used in the model are described in Section 9.1.7 of the submission, with other key features described in Section 9.1.8 (Table 45). The model used a time horizon of 15 years, to ensure that there would be at least one replacement procedure for the HF10 SCS and TR-SCS treatments (Annemans *et al.*, 2014). This is derived from long-term observational data (Kumar *et al.*, 2006a) and was the time horizon of TA 159 (Simpson *et al.*, 2008). The cycle length of the Markov model was 3 months, also consistent with TA 159 (Simpson *et al.*, 2008). The perspective of the model was of a third party payer (the NHS and Personal Social Services [PSS]) and a discount rate of 3.5% was applied to costs and benefits. These are appropriate assumptions (NICE, 2011).

4.2.6 Clinical parameters and variables

The clinical parameters that informed the transition probabilities are described in Section 9.2.1 of the company's submission, and actual values are reported in Table 46. Clinical parameters were derived from the SENZA-RCT (Kapural *et al.*, 2015). For the base case analysis, the company adopted the clinical effectiveness parameters on the reduction of leg pain, rather than back pain. The EAC considered that it was appropriate to select only one type of pain, as they were reported separately in the trial, and an "average" figure would be less meaningful. There was no evidence of bias in the selection of leg pain, as equivalent or possibly larger differential reductions were observed with Senza HF10 treatment with back pain rather than leg pain (Kapural *et al.*, 2016). Back pain values were used in sensitivity analysis (see [Section 4.4.4](#)).

Decision tree

Values calculated from the decision tree set the initial proportions of patients in each clinical state. The EAC has cross-referenced the clinical parameter values, and checked confidence intervals, with the published data wherever possible. The probabilities of trial success (leading to permanent implantation) informing the decision tree are derived from the SENZA-RCT and are consistent with published data (Kapural *et al.*, 2015). The probability of achieving optimal reduction in leg pain ($\geq 50\%$ VAS) at 6 months was also correctly reported from the SENZA-RCT trial, or, in the case of CMM, the PROCESS trial (Kumar *et al.*, 2007).

Patients also 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 unpublished individual-patient analysis of the SENZA-RCT. These data were made available to the EAC and have been independently verified. The company estimated that [REDACTED] of patients had non-serious adverse events at 6 months with Senza HF10, compared with [REDACTED] with low frequency SCS. These data were multiplied by the proportion of people receiving optimal or suboptimal pain relief to give the initial proportions of people with optimal pain relief without complications, optimal pain relief with complications, suboptimal pain relief without complications, and suboptimal pain relief with complications.

Markov model

Clinical parameters informing transition probabilities beyond 6 months are reported in Table 47 and Table 48 of the submission. The proportion of people experiencing non-serious adverse events beyond 6 months was estimated from an individual patient analysis of the SENZA-RCT trial. These data have not been published and cannot be independently verified by the EAC.

In the model, patients receiving SCS cannot leave the pain clinical state they are in (i.e. optimal or suboptimal) except by a serious adverse event occurring requiring irreversible surgical removal of the device (explantation). There were three classifications of serious adverse event that could lead to explantation which were ineffective pain control, intolerable paraesthesia and other adverse events (e.g. surgical site infections, patient falls etc.). Of these, intolerable paraesthesia was specific to low frequency SCS devices. Explantation was a key driver of the model because patients who have devices explanted moved to the CMM side of the Markov model (see [Figure 4.2](#)).

The company has not published the explanation data from the SENZA-RCT study, but reported it as academic in confidence in Table 24 of the submission. This has then informed the first 24 months of the serious adverse event rate. The EAC considered these data should be treated with caution as they were based on low patient numbers and therefore subject to first order uncertainty [REDACTED]. The rate of serious adverse events from 2 years onwards was derived from model used to inform TA 159 (Simpson *et al.*, 2008). This rate was 3.2% (95% CI 0% to 15.8%) for all SCS types and was derived from long-term observational data of low frequency SCS (Kumar *et al.*, 2006a). Other parameters used in the Markov model were also derived from published figures.

Summary

The EAC has validated and cross-referenced the clinical parameters used to derive transitional probabilities in the model where possible. A summary is reported in [Appendix D](#) (Table D4). Many parameters were derived from comparative data in the SENZA-RCT or published sources used to inform TA 159. However, some of the parameters were derived from unpublished data from the SENZA-RCT, including individual patient analyses of adverse events. The EAC has independently corroborated these values and they are consistent with expected values; thus the EAC has not identified any sources of potential bias (see [Section 3.7](#)). Most clinical variables were subject to sensitivity analysis (see [Section 4.4.2](#)).

4.2.7 Model cost parameters

Costs in the model were accrued per cycle in exactly the same way as the model used in the assessment report of TA 159 (Simpson *et al.*, 2008). The costs associated with each clinical state were based on the degree of pain relief achieved (and thus the additional use of CMM) and the presence of complications. There were also costs associated with the device trial, device implantation, explantation, device replacement, and reoperation. A key driver of costs in the model was device longevity, with an assumed useful battery duration of 4 year (range 2 to 6 years) for non-rechargeable implants and 10 years (range 9 to 25 years) for rechargeable technologies. The company has listed the device longevity estimates and the assumptions behind them in Table 49 of the submission. These assumptions were independently verified by clinical experts (NYEAC, 2017). The EAC therefore agrees these estimates and assumptions are reasonable.

The company has reported the costs associated with each clinical state in Section 9.3.7 of the submission (Table 51). Most of the model costs, with the exception of the direct intervention costs (see [Section 4.2.8](#)), were derived directly from the economic model used in TA 159, which were also fully

reported in a later, updated, peer reviewed journal manuscript (Taylor *et al.*, 2010). These costs were originally calculated using bottom up costing techniques but the cost of individual components are not reported. As these costs were dated February 2010, the company inflated the costs using the inflation indices listed in the PSSRU (Personal Social Services Research Unit) Unit Costs of Social Care (Curtis and Burns, 2016). This may not be an appropriate method of cost correction for changes in drug costs (see [below](#)). Inflationary adjustment was conducted clearly in a separate worksheet which the EAC has cross referenced. The pay and prices index rose by 19% between 2010 and 2016. The EAC has listed the costs with comments on what they covered, in [Appendix D](#) (Table D3).

Cost of drug and non-drug therapies

The company included drug and non-drug pain therapy costs in Table 51 of the submission, which were informed by the economic study of Taylor *et al.* (2010). The costs in TA 159 and included bottom up costs for medication including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and anticonvulsants, No drug therapies included physical rehabilitation, psychological rehabilitation, acupuncture, massage, and transcutaneous electrical stimulation of nerves (TENS).

These may have informed the costs used by Taylor *et al.*, (2010). Updating drug costs by a pay and prices index is not judged appropriate as drug prices do not move with general price inflation, but rather factors such as the introduction of competitor products and generic drugs.

Without more information on the components within these bundled costs, their current prices and associated prescription practice, the values adopted for these parameters by the company are a material source of uncertainty within the model. This is tested within the sensitivity analyses (section 4.4.2). As shown in [Figure 4.3](#), the drug costs for CMM are a key cost driver.

Technology and comparator costs

The Senza HF10 system is comprised of an implantable pulse generator (IPG), which forms the bulk of the technology costs, and a range of essential accessory products which vary from person to person depending the nature and location of the pain being treated. The components additional to the IPG include implanted leads, lead extensions, a remote controller, and an external charger. Traditional low frequency SCS systems also consist of an IPG and equivalent components.

The base case technology cost used in the *de novo* economic model of £16,648 was based on the price adopted in the study by Annemans *et al.*

with data from the NHS Supply Chain (catalogue prices commercial in confidence), there was no indication of bias in the device cost values adopted by the company.

Table 4.3. *Direct costs associated with Senza and its comparator.*

	Cost description	Price (95% CI)	Company source	EAC comment
Senza device	Base case price in model	£16,648 (£13,116 to £21,421)	Published cost-effectiveness analysis updated to 2016 prices (Annemans et al., 2014)	This is the full system price only and excludes any consideration of implantation procedural costs. CI values used in deterministic analysis*.
	Reimplantation in model (scenario analysis)	£14,201	Annemans et al. (2014) inflated to 2016 prices. Proportionally reduced to reflect the cost differential between initial and replacement systems for TR-SCS reported in Taylor et al. (2010)	Cost for reimplantation in the model (following battery expiration). Only used in scenario analysis; in the base case the full system price (£16,648) was used
	List price	██████	Company data (commercial in confidence)	Not clear what list price includes (regarding accessories) and assumes no procedure related costs.
	NHS Supply Chain	██████	Company's submission	Complete Senza system price, which includes the implantable pulse generator (IPG), two leads, two extensions, one remote control and one battery charger. Excludes NHS Supply Chain handling fee and VAT.
Comparator	Base case price in model (rechargeable)	£17,422 (£13,726 to £22,418)	TA 159 (Taylor et al., 2010) updated to 2016 prices	This is the full system price only and excludes any consideration of implantation procedural costs. CI values used in deterministic analysis*.
	Base case price in model (non-rechargeable)	£11,281 (£8,888 to £14,516)	TA 159 (Taylor et al., 2010) updated to 2016 prices	
* The derivation of distributional data (confidence intervals) for technologies is unclear.				

4.2.9 Sensitivity analysis

The company employed extensive sensitivity analysis in the model, reported in Section 9.4 of the submission. The EAC considered that the sensitivity analysis performed was appropriate and well conducted. The company employed scenario analysis to test some of the structural assumptions of the

model and deterministic sensitivity analysis to identify key drivers of costs. Additionally probabilistic sensitivity analysis was performed; this is recommended where possible for technical assessments (Claxton *et al.*, 2005). For this analysis, clinical effectiveness and cost parameters were varied using Beta (bounded between 0 and 1) and Gamma (bounded above 0) distributions. Monte Carlo analysis was then run using 5,000 simulations. After each simulation, it was determined if Senza HF10 therapy was cost saving or not; in this way the probability of Senza HF10 being cost saving was calculated.

The sensitivity analyses performed are listed in [Table 4.4](#).

Table 4.4. *Sensitivity analysis employed in de novo analysis.*

Type of sensitivity analysis	Parameters altered/tested	Purpose	EAC comment
Deterministic sensitivity analysis	Initiation of Markov model (3, 6, 12 months)	To test data from SENZA-RCT	Model was based on that of TA 159 which implemented a 6 month decision tree. Primary outcome of SENZA-RCT was 3 months.
	Clinical efficacy of back pain reduction	To use other key outcome of SENZA-RCT.	Base case used leg pain efficacy. It was appropriate to rerun model using back pain outcomes.
Deterministic univariate sensitivity analysis	Examples include: Costs of CMM Cost of device Device longevity Explantation rate	Generate Tornado diagram to identify key sensitivities (cost drivers) in the model.	Univariate analysis was conducted using confidence intervals.
Threshold sensitivity analysis	Top ten most sensitive parameters, as identified by univariate analysis (Tornado diagram).	To identify at which values costs are neutral for Senza HF.	Important threshold for cost saving (e.g. device longevity) identified.
Probabilistic sensitivity analysis	All clinical and cost parameters simultaneously.	To fully incorporate uncertainty present in parameters into cost analysis.	Estimates probability of Senza HF being cost saving.

4.3 Company's interpretation of economic evidence

The company reported the top level base case results of the *de novo* analysis in Section 9.5.1 and 9.5.2 of the submission, a breakdown of the costs in Section 9.5.3 and 9.5.4, costs of adverse events in 9.5.5, and sensitivity analysis in Sections 9.5.6 to 9.5.10. The EAC has spot checked the values stated in these sections with those in the executable economic model and confirmed they are correct.

The *de novo* model was regarded as being of high methodological quality and the EAC was satisfied that the reporting of the results and sensitivity analysis was appropriate and comprehensive. Because of this, the EAC did not rerun any simulations except for purposes of quality assurance. Therefore, for the most part, the EAC has directly interpreted the company's results in [Section 4.4](#).

4.4 Results of EAC analysis

4.4.1 Base-case analysis results

The top level results of the *de novo* economic model, using deterministic analysis and the base case point estimate parameters, are reported in [Table 4.2](#). These results, reported in Section 9.5.2 of the company's submission, showed that, over the 15 year time horizon, Senza HF10 therapy was associated with a saving of £7,775 compared with non-rechargeable low frequency SCS and £4,795 compared with rechargeable low frequency SCS.

The company provided a breakdown of the costs associated with each technology in Section 9.5.3 of the submission. This shows that, compared with rechargeable low frequency SCS (Table 56), Senza HF10 was associated with cost savings in most areas of the patient pathway, namely explantation (due to failed trial or premature removal of permanent device); management of pain and complications; and surgical revisions. Senza HF10 was associated with increased costs of permanent implantation and then reimplantation. This was due to higher initial trial success rates. The comparison with non-rechargeable low frequency SCS yielded similar results with the exception that this technology also incurred additional costs for reimplantation, due to the shorter device longevity (for this reason, non-rechargeable low frequency SCS was the most expensive option). A summary of this breakdown is reported in [Table 4.5](#).

Table 4.5. *Summary breakdown of costs associated with SCS technologies compared with Senza HF10 treatment.*

	Cost (from procedures and medical treatment)	Incremental difference (savings, £)*		EAC comment
		TR-SCS	TNR-SCS	
Decision tree (first 6 months)	Initial trial	£0	£0	Trials were assumed equivalent in costs and were undertaken in all patients.
	Permanent implant (successful trial)	£118	£5,522	Lower costs reflects lower proportion of patients having a successful trial.
	Device explanted (failed trial)	-£103	-£103	Higher costs reflects greater failure rate for LF technologies.
Markov model (6 months to 15 years)	Pain management and complication costs	-£5,328	-£5,439	Patients with poorer response to pain relief use greater CMM resources.
	Reimplantation (planned for replacement)	£894	-£7,359	Large cost for TNR-SCS is because more frequent replacement required.
	Explantation (permanent device failure)	-£114	-£114	LF SCS more likely to require explantation (mainly due to intolerable paraesthesia).
	Surgical revision	-£262	-£262	Device explantation cause patients to enter CMM part of model where surgical revision can occur.
	Total	-£4,795	-£7,755	Top level results (15 year time horizon)
<p>Abbreviations. CMM: conventional medical management; TNR-SCS, traditional low-frequency non-rechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation</p> <p>* Positive values indicate savings compared with Senza HF10, negative values indicate cost expenditure compared with Senza HF10.</p>				

The company reported the breakdown of costs by health states in Table 57 and 58 of the submission. Compared with rechargeable low frequency SCS, more people experienced optimal pain relief and there was a lower incidence of complications throughout the model with Senza HF10. Thus whilst the health states associated with optimal pain reduction had higher costs in the Senza HF10 arm, these were more than offset by savings relating to suboptimal pain relief. Non-rechargeable low frequency SCS reported a similar trend in values.

Patients receiving rechargeable SCS (conventional or Senza HF10 therapy) have a reduced need for device re-implantation (following battery depletion) compared to those receiving non-rechargeable low frequency SCS. This reduces cost in two ways. Firstly, by avoiding the reoperation cost itself, and secondly by avoiding the transient increase in complication risks associated with the implantation of a new device.

The company reported the costs associated with device-related complications in Section 9.5.5 (Table 59 and 60 of the submission). As Senza HF10 treatment was associated with fewer adverse events than either comparator, it was cost saving in this respect.

4.4.2 Sensitivity analysis results

The company reported results of univariate sensitivity analysis in Section 9.5.6 of the submission. The purpose of univariate (one way) sensitivity analysis is to understand the impact that changes in a particular parameter will have on the model's results. For this analysis, the company tested the assumptions of the model by varying one parameter at a time to the plausible extremes of likelihood (that is, the upper and lower limit estimates of the 95% CI). This analysis was considered appropriate by the EAC (NICE, 2011).

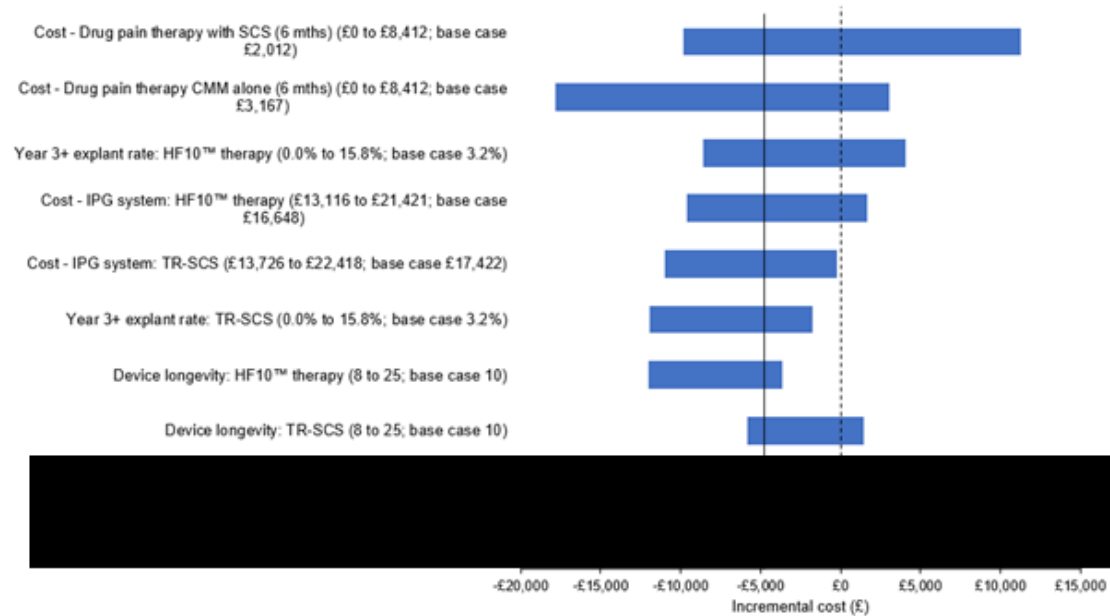
Results comparing Senza HF10 therapy with non-rechargeable low frequency SCS are reported in Table 61 and Figure 30 of the submission, whilst results comparing Senza HF10 therapy with rechargeable low frequency SCS are reported in Table 62 and Figure 31 of the submission (reproduced in [Figure 4.3](#)).

In most cases, the company reported that Senza HF10 therapy was cost saving compared with traditional low frequency SC; that is varying the single parameter estimates to the upper or lower 95% CI still resulted in Senza HF10 being less expensive. The EAC has summarised the parameters which potentially make Senza HF10 the more expensive technology in [Table 4.6](#).

In the opinion of the EAC, the scenarios in which Senza HF10 was cost incurring compared to low frequency SCS were generally not plausible, except possibly the cost of the technology itself (i.e. Senza HF10 device). For instance, the company did not include reduction in procedure time because of the elimination of the need for paraesthesia mapping in their analysis. The clinical experts contacted by the EAC confirmed procedural costs and times were likely to be reduced with the Senza system (NYEAC, 2017). These conservative assumptions provide some reassurance as to the cost saving potential of Senza HF10 therapy.

Figure 4.3. Tornado diagram illustrating sensitivity of the model to single parameter changes of Senza HF10 therapy (using 95% CI intervals) compared with rechargeable low frequency SCS (A) and non-rechargeable SCS (B). Taken from the company's submission.

A. Senza HF10 vs rechargeable low frequency SCS.



B. Senza HF10 vs non-rechargeable low frequency SCS.

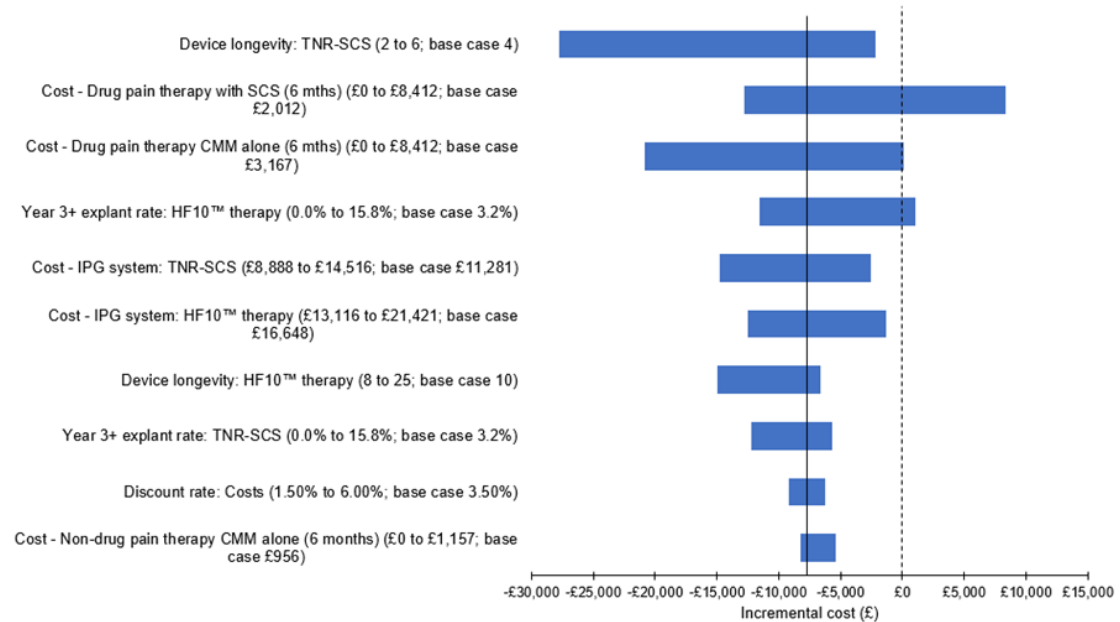


Table 4.6. Univariate analysis which indicates Senza HF10 is potentially cost incurring.

Univariate parameter being tested*.	Potential additional cost expenditure with Senza HF10 therapy**		EAC comment
	TNR-SCS	TR-SCS	
Cost of drug pain therapy with SCS (6 months) Base case £2,012; 95% CI £0 to £8,412.	<i>Upper limit applied</i> HF10 £8,334 more expensive	<i>Upper limit applied</i> HF10 £11,294 more expensive	Primary source of costs was from model used in TA 159 (Taylor <i>et al.</i> , 2010). Upper cost estimate would exceed that for CMM alone which is not plausible.
Cost of drug pain therapy CMM alone (6 months) Base case £3,167; 95% CI £0 to £8,412	<i>Lower limit applied</i> HF10 £123 more expensive	<i>Lower limit applied</i> HF10 £3,083 more expensive	Primary source of costs was from model used in TA 159 (Taylor <i>et al.</i> , 2010). Lower limit assumes no cost for CMM treatment which is not plausible.
Explantation rate associated with HF10 therapy (≥3 years) <u>Base case 3.2%; 95% CI 0.0% to 15.8%</u>	<i>Upper limit applied</i> HF10 £1,079 more expensive	<i>Upper limit applied</i> HF10 £4,038 more expensive	Primary source of costs extrapolated from data from TA 159 (Taylor <i>et al.</i> , 2010). These data were not derived from clinical studies and upper limit appears implausibly high and is not supported by clinical observation.
Cost of Senza HF10 implantation. Base case £16,648; 95% CI £13,116 to £21,421.	N/A (HF10 always less expensive)	<i>Upper limit</i> HF10 £1,676 more expensive	Cost of Senza HF10 derived from previous economic study (Annemans <i>et al.</i> , 2014). Use of 95%CI probably not appropriate.
Device longevity of TR-SCS. Base case 10 years; 95% CI 8 to 25 years.	N/A (HF10 always less expensive)	<i>Upper limit</i> HF10 £1,474 more expensive	Upper limit of 25 years for implant assumes LFSCS significantly outperforming Senza-RCT in terms of device longevity. There is no evidence to support this.
Abbreviations. CI: confidence interval; CMM; conventional medical management; HF10: Senza HF10 therapy; N/A: not applicable; TNR-SCS, traditional low-frequency non-rechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation *95% CI reported in submission. The EAC has not been able to independently verify these distributional data. ** Additional cost associated with Senza HF10 therapy when lower or upper 95% CI limit of tested parameter is applied.			

4.4.3 Threshold analysis

The company performed threshold analysis on parameters identified as potentially sensitive in the univariate analysis. The purpose of threshold analysis is to calculate at which point the cost of the technology becomes cost neutral after adjustment of the parameter value. This analysis is of interest as Senza HF10 therapy has demonstrated superiority in delivering patient benefits and therefore only needs to demonstrate cost neutrality in order to meet the principles set out by MTEP (NICE, 2011).

The top ten parameters identified as most sensitive by the univariate analysis are reported in Table 63 (comparison with non-rechargeable low frequency SCS) and Table 64 (comparison with rechargeable SCS). The EAC has summarised the threshold analysis on the key parameters of uncertainty in [Table 4.7](#). Less tangible parameters which cannot be easily appraised or measured, such as the costs associated with a clinical state, or parameters that generate negative values, have been omitted.

The two key areas of uncertainty identified were the associated costs of the implanted technologies (including procedural and device costs) and device longevity. Threshold analysis indicated that Senza HF10 technology was cost neutral at an implant price of approximately £21,000 and device longevity of around 7 years. Conversely, if the implantation cost of rechargeable low frequency SCS fell below £13,500 or if this technology could remain *in situ* for around 15 years (compared with 10 years for Senza HF10) then Senza HF10 was the more costly option.

Table 4.7. *Threshold analysis of key parameters used in model.*

Parameter being tested for threshold analysis	Technology	Value that gives cost neutrality	
		Non-rechargeable low frequency SCS	Rechargeable low frequency SCS
Device longevity*	Low frequency SCS	7.5 years	15.25 years
	Senza HF10	N/A	6.75 years
Cost of implantation**	Cost of technology (comparator)	£7697	£13,547
	Senza HF10	£22,368	£20,185
<p>* Due to quarterly cycle length, this value indicates when Senza HF10 first becomes cost incurring rather than cost saving.</p> <p>** Cost of implantation includes technology costs and procedural costs. It does not include trial costs which are assumed equivalent between technologies in the model.</p>			

4.4.4 Scenario analysis

The company reported two scenario analyses in Section 9.5.7 of the submission. In the first analysis, the model was repeated using data from the SENZA-RCT for back pain response, rather than leg pain (Kapural *et al.*, 2015). The SENZA-RCT reported a response rate of 76.4% for back pain reduction at 6 months compared with 51.9% for low frequency SCS. This response was lower for both interventions compared with leg pain response (80.9% and 54.4% respectively). However, the relative ratio (RR) of the response was the same in both scenarios (1.5 [95%CI 1.2 to 1.9]) for back pain and (1.5 [95% CI 1.2 to 1.9]) for leg pain. The cost saving potential of Senza HF10 was calculated as £7,755 compared with non-rechargeable low frequency SCS and £4,795 compared with rechargeable low frequency SCS. This was identical to the base case (see [Table 4.5](#)).

In the second analysis, the company used alternative leg pain outcomes from the SENZA-RCT at 3, 12 months (Kapural *et al.*, 2015), and 24 months (Kapural *et al.*, 2016b), rather than 6 months used in the base case. The data inputs used are reported in Table 67 of the submission. Altering the inputs has only a marginal effect on the final cost outcomes.

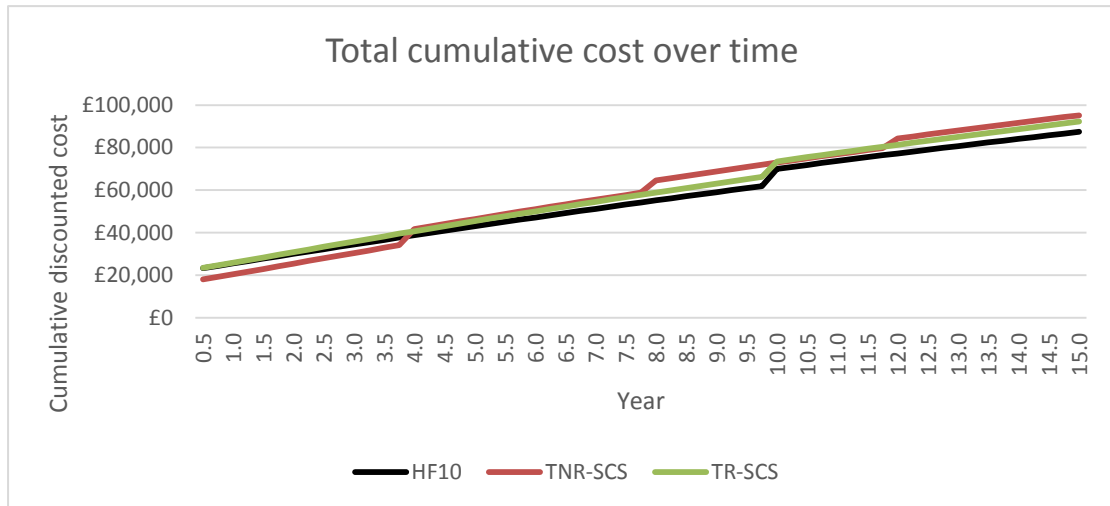
4.4.5 Time horizon

The company analysed at which time point Senza HF10 would become cost saving. Compared with rechargeable low frequency SCS, Senza HF10 was cost saving from the outset, due to marginally lower acquisition costs. Non-rechargeable SCS was cost saving compared with Senza HF10 therapy initially, but became cost incurring at 4 years (time of re-implantation of non-rechargeable technology). Differences in total cumulative and incremental costs are illustrated in Figure 4.5 (taken from company model). It can be seen

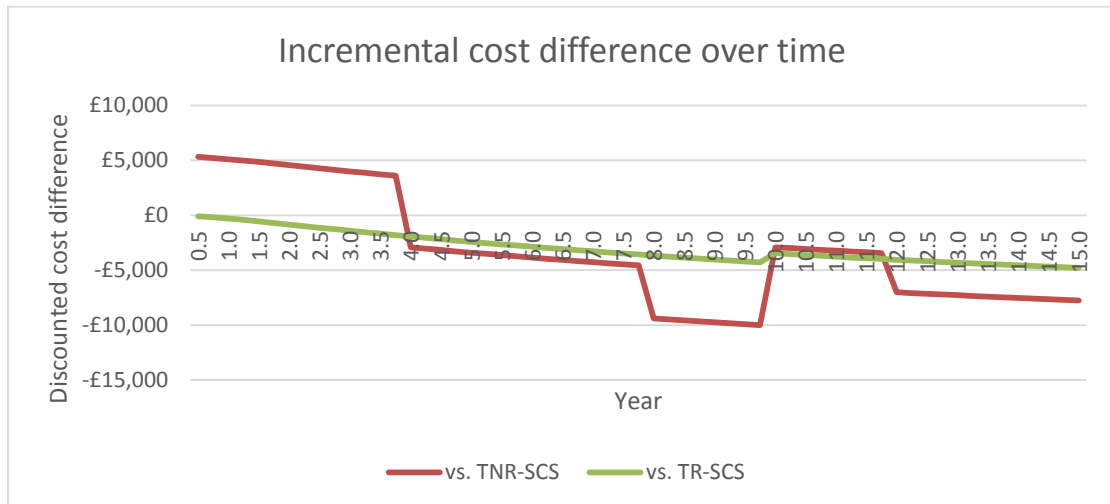
that total cumulative costs are similar, although incremental analysis favours Senza HF10 therapy.

Figure 4.5. Comparison of cumulative (A) and relative (B) costs of Senza HF10 and low frequency SCS technologies over time.

A. HF10 vs. non-rechargeable low frequency SCS (TNR-SCS) vs. rechargeable low frequency SCS (TR-SCS).



B. HF10 vs. non-rechargeable low frequency SCS (TNR-SCS).



4.4.6 Alternative system costs

The company provided additional analysis including two assumptions regarding the cost of Senza HF10 technology compared with traditional rechargeable low frequency SCS: these were that re-implantation was marginally less expensive than initial implantation, in accordance with the model used in TA 159 (Taylor *et al.*, 2010); and that both technologies had the same cost. The company stated the latter assumption was conservative as in the base case rechargeable low frequency SCS was slightly more expensive than Senza HF10 therapy. The results from this analysis were largely unchanged from base case.

In Section 9.5.8 of the submission, the company performed a scenario analysis using national tariff prices (using Healthcare Resource Group [HRG]). As national tariffs did not have cost differentials between the technologies, there was little difference from the base case analysis in terms of rechargeable low frequency SCS, although the incremental cost of non-rechargeable low frequency was increased from £7,755 to £9,687.

4.4.7 Probabilistic sensitivity analysis

The company reported the results of the PSA in Section 9.5.9 of the submission. The results are summarised in Table 4.8.

Table 4.8. Results of PSA for the *de novo* model.

Technology	Probability Senza HF10 is cost saving*	Expected (mean) cost savings associated with Senza HF10*
Rechargeable low frequency SCS	73%	£3,552 (95% CI £3,313 to £3,972)
Non-rechargeable low frequency SCS	74%	£7,170 (95% CI £6,767 to £7,573)
* Calculated from 5,000 simulations. Results will vary slightly each time simulation is run.		

Thus it can be seen that in approximately three quarters of simulations, Senza HF10 therapy was found to be cost saving compared with either of the comparators. The use of PSA, in addition to the deterministic sensitivity analysis performed, provided additional confidence that the model outcomes

were robust and that parameter uncertainty was unlikely to change the direction of results (Briggs *et al.*, 2012).

4.4.8 Subgroup analysis

The company elected not to perform subgroup analysis, because there was a lack of robust clinical evidence to inform such analysis ([Section 2.2](#)). The EAC agreed with this decision. Therefore, the results from the economic model should be considered to apply to patients who share the characteristics of those in the SENZA-RCT study (patients with back and leg pain of suspected neurological origin) (Kapural *et al.*, 2015). Specifically, this includes patients with and without FBSS, but not patients with neurological pain involving the head, neck, and upper limbs, or patients with CRPS.

4.4.9 Model validation

In Section 9.7.1 of the submission, the company stated “The data inputs were cross-checked and the model calculations were verified by a second health economist”.

The EAC has extensively cross-referenced the model inputs from the original sources, where possible and independently quality assured the Excel model using appropriate tools and checklists.

The EAC also used an in-house Markov solver to independently replicate the company’s Excel model in terms of patient flow. The EAC solver, written in R statistical computing language (R Core Team, 2013), uses the Monte Carlo approach, in which patients are followed through the model and make random transitions between states (based on transition probabilities) using a random number generator. This differs from the company’s Excel model, which directly calculates proportions. The Monte Carlo approach gives slightly different results each time, but with sufficient patients or runs of the model, these fluctuations are small. The EAC Markov solver was used to simulate 1000 patients having HF10 therapy, with 11 states (separate complication states), four cycles per year, over 25 years with different device failure rates in years one, two and afterwards. After 25 years, the total number of patients with SCS (four states) was 328, the total with CMM (four states) was 491, the number in the final cycle having explant was one, and 180 patients were dead. Senza’s proportions (in the Excel tab ‘PtFlow_HF10’) were 32.8%, 0.3%, 48.9% and 18.1% respectively. Thus in terms of gross patient flows, the two models agree. It should be noted that this approach would not identify any discrepancies in the proportions having a complication.

4.5 EAC Interpretation of economic evidence

The principal evidence to support the cost saving potential of the Senza HF10 system was provided by the company's *de novo* model. The EAC considered that the model itself, as well as the accompanying submission, was of a high methodological standard. The model had several strengths which made it robust.

The main strength of the model was that it adopted the same structure as a previous decision analytic model used to inform NICE TA 159 (Simpson *et al.*, 2008). This model has been peer reviewed and published in a journal (Taylor *et al.*, 2010) and as an NIHR (National Institute for Healthcare Research) Technology Assessment (Simpson *et al.*, 2009). Additionally, the economic analysis by Annemans, based on the same model, has also been peer reviewed and published in a journal (Annemans *et al.*, 2014). The model also used clinical data from the pivotal RCT (SENZA-RCT). Thus, the structure and inputs of the model have already been scrutinised and accepted by experts and decision making bodies.

Other strengths of the *de novo* model include its consistent use of conservative assumptions which have been verified as such by clinical experts. The model employed extensive deterministic sensitivity analysis to test these assumptions and uncertainties and reported these using appropriate graphical displays. In particular, the use of appropriate distributions for each parameter within the PSA adds to the overall robustness of the model results and lends some certainty to the conclusions drawn. Although the model was developed as a cost-utility analysis, the company has focussed on the cost saving potential of the technology. However, improved patients benefits should not be disregarded (see [Section 5.1](#)).

The model has some weaknesses or limitations, which are unavoidable when the clinical evidence base is not complete. Some of the transition probabilities, for instance the device explantation rate, were based on low event rates (numerator) and relatively low sample sizes (denominator). The EAC also noted that the evidence from the clinical trials used to inform the original TA 159 model were limited in quality and there was considerable uncertainty in the interpretation of their results (North *et al.*, 2005; Kumar *et al.*, 2007). This uncertainty was compounded by the fact the model had time horizon of 15 year, which required extrapolation of the data well beyond the time of the trial follow up.

Regarding costs, the model conservatively assumed procedural costs were equivalent for each technology. However, the costs of the drug therapy and non-drug therapy to manage pain could not be validated and these were key drivers of the model. Non-drug costs were inflated to 2016 values, but this

might not take into account changes to the clinical pathways and clinical practice that have taken place since TA 159 was first authored. The cost of drugs may also have changed, for instance, as a result of the introduction of generic compounds or increased use of proton pump inhibitors (in combination with NSAIDs). Additionally, some surgical techniques are now actively not recommended by NICE (NICE, 2016). Finally, the clinical data used in the model was specific to people with back and/or leg pain of suspected neuropathic origin, and thus cannot be generalised to other populations.

The EAC considered the model and inputs were of a sufficient standard that no additional work was required to refine the model further. Instead, the EAC has comprehensively reviewed the *de novo* model and quality assured its inputs and outputs, and reported its findings.

The base case analysis of the model reported that the use of Senza HF10 is cost saving compared to traditional low frequency SCS technologies. If Senza HF10 therapy was used instead of an equivalent rechargeable low frequency SCS technology, estimated savings were £4,795 per patient over a 15 year period. If Senza HF10 therapy was used instead of a non-rechargeable low frequency SCS technology, estimated savings were £7,755 per patient. The EAC understands from clinical experts that, in the UK, most implants are non-rechargeable (NYEAC, 2017).

Extensive sensitivity analysis, including PSA, did not change the direction of cost savings except in implausible scenarios. Therefore, the EAC concludes that the appropriate adoption of Senza HF10 therapy, in the population indicated by TA 159, would be cost saving for the NHS compared to current practice.

5 Conclusions

5.1 Conclusions on the clinical evidence

The company provided a comprehensive clinical evidence submission in support of its claims for the efficacy and safety of the technology, the Senza HF10 SCS system. The submission was rigorous and clearly written, and correctly addressed all elements of the submission template.

The pivotal study identified by both the company and the EAC was the SENZA-RCT study (Kapural *et al.*, 2015; Kapural *et al.*, 2016b). This was a non-inferiority RCT (n = 198) that compared the use of Senza HF10 therapy with traditional low frequency SCS (Precision Plus System, Boston Scientific) in a population broadly consistent with TA 159, with a follow up of 2 years. The study reported that the Senza HF10 was associated with a significantly

improved pain reduction, with 84.3% and 83.1% of patients responding to Senza HF10 for back and leg pain respectively at 3 months, compared with 43.8% and 55.0% for low frequency SCS ($p < 0.001$). This differential effect persisted for at least 2 years. There were also significant comparative improvements in patient disability measures such as ODI measurement, as well as patient satisfaction.

The EAC critically appraised the SENZA-RCT and identified the potential for performance, detection, and reporting bias. There was some inconsistency in the denominator used in the reporting of results. However, overall the EAC was satisfied that the trial's limitations and weaknesses were not of sufficient magnitude to affect the direction of results reported. As there has been trial evidence published that has shown traditional low frequency SCS has improved benefits compared with CMM (Kumar *et al.*, 2007) and reoperation (North *et al.*, 2005), the EAC felt confident that the Senza HF10 system was associated with a clinically meaningful sustained effect and related patient benefits.

The other studies, which were all single-armed and observational (with the exception of Tiede *et al.* [2013]) reported non-comparative data that generally supported the SENZA-RCT, and thus gave confidence in the overall results. The most important of these was the SENZA-EU study (Van Buyten *et al.*, 2013) which reported outcomes at 2 years (Al-Kaisy *et al.*, 2014). Observational data also confirmed that patients are able to drive (or operate machinery) with Senza HF10 therapy.

The EAC considered that the evidence was generalisable to patients in the NHS eligible for low frequency SCS, as defined in TA 159. However, this applied to patients with neuropathic leg and back pain only, and should not be extrapolated to other conditions (such neuropathic pain of the head, neck, or upper limbs, or CRPS).

Although the SENZA-RCT provided good comparative evidence for the efficacy and safety of Senza HF10, there remain some gaps in the evidence base. This includes a need for longer term studies, and comparisons with a sham so the magnitude of the placebo response can be addressed.

5.2 Conclusions on the economic evidence

The company and the EAC identified one published economic study that was within scope. This was a cost utility analysis that compared Senza HF10 therapy with rechargeable and non-rechargeable low frequency SCS, CMM, and reoperation (Annemans *et al.*, 2014). This study reported that Senza HF10 therapy was cost effective compared with CMM and reoperation, and dominated the low frequency SCS technologies.

The company presented a *de novo* economic model that was based on the decision analytic model used to inform TA 159 (Simpson *et al.*, 2008), which has since been published in a peer reviewed journal (Taylor *et al.*, 2010) and was the basis of the Annemans study. The model was fully executable and the EAC was able to fully quality assure its structure and inputs using appropriate checklists and cross-referencing values to original sources.

The company reported a base case scenario with deterministic analysis. In addition, the company tested the assumptions used with extensive univariate, threshold, and scenario sensitivity analyses, as well as PSA. This analysis provided confidence in the model's results.

In the base case, Senza HF10 therapy was associated with an incremental saving of £4795 per patient compared with rechargeable low frequency SCS after 15 years. This increases to £7755 per patient when compared against non-rechargeable technology, which is currently more commonly used in the NHS (NYEAC, 2017). These saving are relatively modest (approximately £320 and £500 per annum, accounting for 5% and 8% of total costs) but are probably conservative, and do not take into account increased patient benefit.

Extensive deterministic sensitivity analysis showed that Senza HF10 was cost saving except when less plausible scenarios or inputs were used. When PSA was used, it was found that Senza HF10 was cost saving in about three quarters of simulations. The EAC's main concern relates to the values assumed for the cost of pain management given the lack of transparency on the resources used to manage pain or their unit costs. The sensitivity analyses show the results are sensitive to this value. However, results from adopting a range of credible potential values suggest the Senza HF10 remains cost-saving.

The EAC was thus satisfied that Senza HF10 is cost saving compared with current practice and its implementation into the NHS should release healthcare resources.

6 Summary of the combined clinical and economic sections

The clinical evidence to support the Senza HF10 system is largely derived from a non-inferiority RCT (n = 198) which compared the technology with low frequency SCS over a period of 2 years. The trial reported that Senza HF10 therapy was associated with statistically significant and clinically important reductions in back and leg pain compared with traditional SCS. Senza HF10 therapy was also associated with reduced patient disability and improvements in quality of life, as well as allowing patients to drive. Although some sources of bias were identified, overall the EAC considered these would not materially impact on the large and sustained clinical effects observed. Longitudinal data

from the SENZA-RCT was also supported by observational data from single-armed studies.

The company provided a fully executable *de novo* model, the structure of which, and many inputs, had already been validated in NICE TA 159. The EAC considered the model was robust, and this was demonstrated through extensive deterministic sensitivity analysis and PSA. The model reported estimated savings from Senza HF10 of £4,795 per patient compared to rechargeable low frequency SCS and nearly £7,755 per patient compared with non-rechargeable low frequency SCS over the 15 year time horizon. It was cost saving in three quarters of simulations.

In summary, the EAC concludes that Senza HF10 therapy is associated with clinically important reductions in pain for up to 2 years in people with neuropathic back and/or leg pain, as well as reductions in associated disabilities and, based on economic modelling, is likely to be cost saving for the NHS.

7 Implications for research

The evidence for the efficacy and safety of Senza HF10 therapy has been largely established by the SENZA-RCT study (Kapural *et al.*, 2015), which reported superiority over traditional low frequency SCS with a follow up of 2 years (Kapural *et al.*, 2016b). A limitation of this trial was that it did not include a “no SCS” (i.e. CMM only) or a sham treatment (placebo) arm. The EAC considers that it would be of considerable value for such a trial to be undertaken so the influence of non-specific factors, such as the placebo effect on pain perception, could be better understood. Sham controlled trials involving the Senza system have been proposed previously, or are reported as currently on-going (see [Section 3.8](#)), but as yet have not been published in a peer reviewed journal. The EAC accepts that a sufficiently powered, high quality, RCT would be very expensive to undertake and may require industry support, which may limit its practical application.

The SENZA-RCT and SENZA-EU studies were limited to 2 years follow up, with other identified studies have shorter follow up. However, chronic neuropathic back and leg pain represent long-term, possibly life-long, morbidities. For this reason, longer-term studies on efficacy are required. Practically, these could be observational studies or registries.

Finally, evidence from the SENZA-RCT was restricted to patients with neuropathic pain of the back and/or leg. If recommendations are to be extended to other patient groups, such as those with neuropathic head, neck, upper limb pain, or CRPS, then research needs to be conducted in these populations. The EAC notes that company-sponsored research into the use of

Senza HF10 therapy in patients with intractable pain of the arms and neck is currently on-going (NCT02365201; NCT02703818).

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Appendix A: Literature searches and evidence selection.

A1: Critique of the company's search methods

The Peer Review of Electronic Search Strategies (PRESS) Checklist was used to inform the critique of the company's search strategies (McGowan *et al.*, 2010). The PRESS checklist is an evidence-based tool used to critically appraise literature search strategies. The PRESS project was funded by the Canadian Agency for Drugs and Technologies in Health (CADTH) and this approach to peer reviewing search strategies is supported by the Cochrane Collaboration's Information Retrieval Methods Group (Sampson *et al.*, 2008).

Search reporting

The company clearly states which bibliographic databases were used for the searches (Sections 7.1.1 and 8.1.1, Submission), although it is not clear which segment of the Cochrane Library was searched. Although the search for ongoing studies is reported in Section 5.1 rather than the main sections on search methodology, the details do include the URLs for the registers searched. It is not clear however which interfaces were used for the register searches. The Medical Technologies Evaluation Programme (MTEP) Submission Template states that the strategies used to retrieve relevant clinical data from the published literature and unpublished sources should be clearly described in sufficient detail to enable the methods to be reproduced. The search strategies for bibliographic databases and trial registers are reported but are not described in sufficient detail to enable fully confident reproduction. A hand-search of internal documentation to identify unpublished studies is reported (Sections 7.1.2 and 8.1.5, Submission) but no further details are given on the content of the internal documentation or the hand-search methods used. It is therefore not possible to comment on the content of this documentation, or the appropriateness of the hand-search methods used. Search result numbers are given for the bibliographic database searches, but not for the trials register searches (where just the number of identified relevant results is given). Search result numbers for the hand-search of internal documentation are not clear. In section 7.1 the company states that the hand-search identified 46 published conference abstracts. This is not reflected however in the schematic for the systematic literature review and hand-searching of the manufacturer's internal documentation (Section 7.2.2, Figure 4, Submission) where the only reference to the hand-search indicates that 3 unpublished studies were found. Search dates are given for the bibliographic database searches, but not for the trial register searches or the hand-search of internal documentation.

Search sources

The company searched all the resources indicated as a minimum requirement in the NICE submission template (MEDLINE, MEDLINE In-Process, Embase, and the Cochrane Library). In addition, the company also searched Scopus. Scopus is a multidisciplinary database; its inclusion in the company's search sources enhances the range of resources searched. The resources searched by the company for published studies represent a good selection of core bibliographic databases indexing healthcare research.

The NICE MTEP Methods guide specifies that search sources should include conference proceedings. The company conducted a hand-search of internal documentation to identify unpublished studies, but the retrieved conference abstracts were not reported in the submission as they were deemed to not add any additional evidence to that presented (Section 7.1, Submission). The submission eligibility criteria specifically excludes conference abstracts. The appropriateness of the company's eligibility criteria is discussed in [Section 3.2](#). No further searches for conference proceedings were carried out (for example, searches of conference proceedings databases or hand-searches of specific conference proceedings) and conference abstracts were excluded from all the Embase searches.

The MTEP Methods guide indicates that search sources should include registers or databases of ongoing clinical trials. In section 5.1 a search of two key trials registers (the ISRCTN registry and ClinicalTrials.gov) is reported. The submission search methodology would have been enhanced by searching additional trials registers as suggested by methods guidance, in particular the WHO International Clinical Trials Registry Platform (ICTRP) which includes data-sets from 3 international registers and 14 national registers.

Bibliographic databases: search strategy structure, search terms, syntax and restrictions

The search methods reported in the submission do not contain sufficient detail to be certain of the exact search strategies used, but enough information was provided for the EAC to make an informed judgement as to how the searches were conducted (for further details see Appendix A2) and the search strategies were critiqued on this basis.

The approach taken by the company to search strategy construction does not reflect conventional approaches to systematic literature review searches. Rather than conducting one single search for each database, the reported

methods indicate that for each database a number of short, separate searches were carried out, with limits applied separately to each search and results collected separately. In addition, rather than explicitly including distinct subject heading searches and free text searches across specific fields in databases such as PubMed and Embase, the company just searches across 'all fields'. The restriction of the 'spinal cord stimulation' search terms in the Cochrane Library searches to "title, abstract, key words" fields was not appropriate. Restricting in this way risks missing records in Cochrane Library databases such as Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment Database (HTA) as (counter-intuitively) a search limited to the abstract field in the Cochrane Library does not search for the terms in DARE and HTA 'abstracts'.

The search terms included in the bibliographic database strategies were appropriate, though limited in range given the systematic review context. No spelling errors were identified and the use of Boolean operators to combine terms was appropriate. The limited range of variant terms potentially increased the risk of missing relevant studies. Search methodology would have been enhanced, for example, by including additional free-text terms to retrieve potential variants for the spinal cord stimulation concept (such as stimulation of the spinal cord, spinal cord electrostimulation/s, spinal cord stimulator/s and SCS). Similarly, search terms for the high frequency concept would have been enhanced by including potential free-text variants such as HF10, HF-10, 10khz and 10 kilohertz. No truncation was used; methodology would have been enhanced by the appropriate use of truncation, for example to search for variants of the device trade name such as SenzaTM.

Date, language and human study limits were applied to some of the bibliographic database searches, though not to all. No rationale is given for this inconsistency. As the submission does not contain sufficient detail to be certain of the exact search strategies, it is not possible to tell if the date, language and human study limits were applied correctly. Where date and language limits are applied, searches are limited to results published in English from 2006, reflecting the submission eligibility criteria. The appropriateness of the company's eligibility criteria is discussed in [Section 3.2](#). Where search results are limited to human studies, the strategies appear to limit to records which are indexed as human studies. This approach is not optimal - by restricting strategies using the 'Human' limit the company risks excluding records which are not fully indexed yet, or where the indexer has not used the Humans subject heading. The submission search methodology would have been enhanced by using the standard safer algorithm of (results NOT (animals NOT human)).

The company's strategies include only terms for the intervention, and do not restrict by combining these with terms for additional concepts (for example population, study design or outcomes). This was an appropriate, sensitive approach to search structure given the low result numbers. Some publication types (letters, reviews, book chapters, conference abstracts or conference reviews) are excluded from some of the searches, but not all of the searches. No rationale is given for the different approaches used to publication type exclusion. Where applied, the publication type exclusions reflect the submission eligibility criteria. The appropriateness of the company's eligibility criteria is discussed in [section 3.2](#). By excluding these study types at the search stage however, the company removes publication types (such as systematic reviews and letters) from the assessment process which can act as an additional source for identification of relevant primary studies. The company's search methodology might have been enhanced by not excluding some of these publication types at search stage, particularly reviews.

Trials registers: search strategy structure, search terms, syntax and restrictions

The search terms used by the company are appropriate, though limited in range given the systematic review context (as with the bibliographic database strategies). In addition, whilst the bibliographic database searches include the term '10 khz', the registry searches do not. No explanation is given for this difference. As with the bibliographic database searches, the limited range of variant search terms potentially increases the risk of missing relevant studies. Search methodology would have been enhanced by including a wider range of variant terms. For the terms which are included, no spelling errors were identified and though reporting is not fully clear it seems that the single Boolean operator is used correctly.

Currency of searches

The bibliographic database searches were conducted in December 2016, almost 6 months before the submission. A gap between search date and review completion is inevitable in any systematic review, but obviously relevant studies may have been published or added to the databases in this period. No search date is given for the trial register searches or the hand-search of internal documentation therefore it is not possible to ascertain currency for these searches.

A2: Re-run of the company's searches

As previously noted, the search methods reported in the submission do not contain sufficient detail to be certain of the exact search methods used, but enough information was provided for the EAC to make an informed judgement as to how the searches were conducted, and the searches were re-run on this basis. The EAC assumed that the top line of the table reporting each database search (e.g. "Title, abstract, key words" AND "All text") indicated the respective fields the company searched across in each of the search lines which followed. So, for example, for the search line "spinal cord stimulation" AND "high frequency" the EAC assumed that if the top line in the table stated "Title, abstract, key words" AND "All text" this meant that "spinal cord stimulation" was searched across the title, abstract, and key words fields, and was combined using Boolean AND with "high frequency" searched across all text. We also assumed that the correct syntax had been used for field searches and for applying restrictions to the search terms (for example date, language, human, publication type).

The EAC searched Embase via the Ovid interface; the company's Elsevier Embase strategies were translated for Ovid as appropriate.

Re-run company's searches: information resources

The information resources searched for the re-run company's searches are shown in Table A2.1.

Table A2.1: *Re-run company's searches: databases and information resources searched*

Database / information resource	Interface / URL
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	OvidSP
Embase	OvidSP
Cochrane Library (all databases)	Cochrane Library / Wiley
Scopus	Scopus.com
ClinicalTrials.gov	https://clinicaltrials.gov/
ISRCTN registry	http://www.isrctn.com/

Results of the searches were downloaded and imported into EndNote reference management software. The records were deduplicated using several algorithms.

Re-run company's searches: results

The search identified retrieved 583 records, with 314 records remaining for assessment after deduplication (Table B2).

Table B2: Re-run company's searches: results

Database / information resource	Records identified
PubMed	160
Cochrane Library (all databases)	53
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	27
Embase	136
Scopus	172
ClinicalTrials.gov	26
ISRCTN registry	9
TOTAL	583
TOTAL after deduplication	314

Re-run company's searches: full search strategies

A.1: Source: PubMed

Interface / URL: <https://www.ncbi.nlm.nih.gov/pubmed/>

Database coverage dates: 1946 to current. Updated daily.

Search date: 08/06/17

Retrieved records: 160

Search strategy:

The following 4 searches were carried out separately using the advanced search interface. The search terms was searched across 'All Fields' (selected using the drop-down menu in the Builder). Results were downloaded and imported into EndNote separately.

Search 1: 123 records retrieved

#4 Search ((spinal cord stimulation) AND high frequency) Filters: Publication date from 2006/01/01 to 2016/12/19; Humans; English 123

#3 Search ((spinal cord stimulation) AND high frequency) Filters: Humans; English 206

#2 Search ((spinal cord stimulation) AND high frequency) Filters: Humans 224

#1 Search ((spinal cord stimulation) AND high frequency) 748

Search 2: 30 records retrieved

#2 Search ((spinal cord stimulation) AND 10 khz) Filters: Publication date from 2006/01/01 to 2016/12/19 30

#1 Search ((spinal cord stimulation) AND 10 khz) 49

Search 3: 4 records retrieved

#1 Search ((spinal cord stimulation) AND neuro) 4

Search 4: 3 records retrieved

#1 Search ((spinal cord stimulation) AND senza) 3

A.2: Source: The Cochrane Library

Database coverage dates: Cochrane Database of Systematic Reviews: Issue 6 of 12, June 2017; Database of Abstracts of Reviews of Effects: Issue 2 of 4, April 2015; Cochrane Central Register of Controlled Trials: Issue 5 of 12, May 2017; Cochrane Methodology Register : Issue 3 of 4, July 2012; Health Technology Assessment Database: Issue 4 of 4, October 2016; NHS Economic Evaluation Database : Issue 2 of 4, April 2015; About the Cochrane Collaboration : Issue 5 of 12, May 2017

Interface / URL: Cochrane Library / Wiley

Search date: 08/06/17

Retrieved records: 53

Search strategy:

The following 4 searches were carried out separately using the advanced search interface. Search fields were selected using the drop-down menu in the advanced search interface. Date limits were selected using the Search Limits option. Results were downloaded and imported into EndNote separately.

Search 1: 25 records retrieved

"spinal cord stimulation" [*Title, abstract, keywords* selected]

AND

"high frequency" [*Search all text* selected]

Publication Year from 2006 to 2016 [*Limit applied*]

= 25 records (all in Cochrane Central Register of Controlled Trials : Issue 5 of 12, May 2017; 0 records retrieved in other Cochrane Library databases)

Search 2: 19 records retrieved

"spinal cord stimulation" [*Title, abstract, keywords* selected]

AND

"10 khz" [*Search all text* selected]

Publication Year from 2006 to 2016 [*Limit applied*]

= 19 records (all in Cochrane Central Register of Controlled Trials : Issue 5 of 12, May 2017; 0 records retrieved in other Cochrane Library databases)

Search 3: 1 record retrieved

"spinal cord stimulation" [*Title, abstract, keywords* selected]

AND

nevro [*Search all text* selected]

= 1 record (in Cochrane Central Register of Controlled Trials : Issue 5 of 12, May 2017; 0 records retrieved in other Cochrane Library databases)

Search 4: 8 records retrieved

"spinal cord stimulation" [*Title, abstract, keywords* selected]

AND

senza [*Search all text* selected]

= 8 records (in Cochrane Central Register of Controlled Trials : Issue 5 of 12, May 2017; 0 records retrieved in other Cochrane Library databases)

**A.3: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
June 07, 2017**

Interface / URL: OvidSP

Database coverage dates: Updated Daily

Search date: 08/06/17

Retrieved records: 27

Search strategy:

The following 4 searches were carried out separately. Results were downloaded and imported into EndNote separately.

Search 1: 16 records retrieved

1 (spinal cord stimulation and high frequency).af. (17)

2 limit 1 to yr="2006 -Current" (16)

Search 2: 6 records retrieved

1 (spinal cord stimulation and 10 khz).af. (6)

2 limit 1 to yr="2006 -Current" (6)

Search 3: 3 records retrieved

1 (spinal cord stimulation and nevro).af. (3)

Search 4: 2 records retrieved

1 (spinal cord stimulation and senza).af. (2)

A.4: Source: Scopus

Interface / URL: Scopus.com

Database coverage dates: Information not found

Search date: 08/06/17

Retrieved records: 172

Search strategy:

The following 4 searches were carried out separately. Search fields were selected using the drop-down menu. Limits were selected using the options available on the Document results page. Results were downloaded and imported into EndNote separately.

Search 1: 105 records retrieved

TITLE-ABS-KEY ("spinal cord stimulation") AND ALL ("high frequency") AND (LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006)) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Human")) AND (EXCLUDE (DOCTYPE , "re")) = 105 records

Search 2: 40 records retrieved

(TITLE-ABS-KEY ("spinal cord stimulation") AND ALL ("10 khz")) AND (LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012)) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (DOCTYPE , "re")) = 40 records

Note: no options to limit prior to 2012 – no records with a publication date before this

Search 3: 8 records retrieved

(TITLE-ABS-KEY ("spinal cord stimulation") AND ALL (nevro)) AND (LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 1997)) AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "ch")) = 8 records

Note: no options to limit to other publication years – no records with a publication date outside these years.

Search 4: 19 records retrieved

(TITLE-ABS-KEY ("spinal cord stimulation") AND ALL (senza)) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "ch")) = 19 records

A.5: Source: Embase

Interface / URL: OvidSP

Database coverage dates: 1974 to 2017 June 7

Search date: 08/06/17

Retrieved records: 136

Search strategy:

The following 4 searches were carried out separately. Results were downloaded and imported into EndNote separately.

Search 1: 79 records retrieved

- 1 (spinal cord stimulation and high frequency).af. (258)
- 2 limit 1 to yr="2006 - 2016" (227)
- 3 (conference abstract or conference review or letter or review).pt. (5807731)
- 4 2 not 3 (79)

Search 2: 30 records retrieved

- 1 (spinal cord stimulation and 10 khz).af. (109)
- 2 (conference abstract or letter or review).pt. (5807731)
- 3 1 not 2 (30)

Search 3: 14 records retrieved

- 1 (spinal cord stimulation and nevo).af. (64)
- 2 (conference abstract or review).pt. (4831332)
- 3 1 not 2 (14)

Search 4: 13 records retrieved

- 1 (spinal cord stimulation and senza).af. (44)
- 2 (conference abstract or review).pt. (4831332)
- 3 1 not 2 (13)

A.5: Source: ClinicalTrials.gov

Interface / URL: <https://clinicaltrials.gov/>

Database coverage dates: Information not found.

Search date: 09/06/17

Retrieved records: 26

Search strategy:

The following 3 searches were carried out separately, using the homepage search interface. Results were downloaded and imported into EndNote separately.

Search 1: nevro = 5 records

Search 2: senza = 7 records

Search 3: "high frequency" AND "spinal cord stimulation" = 14 records

A.5: Source: ISRCTN registry

Interface / URL: <http://www.isrctn.com/>

Database coverage dates: Information not found.

Search date: 09/06/17

Retrieved records: 9

Search strategy:

The following 3 searches were carried out separately, using the homepage search interface. Results were downloaded and imported into EndNote separately.

Search 1: nevro = 8 records retrieved

Search 2: senza = 0 (6 records found – all 6 were duplicates of records already found, so were not retrieved)

Search 3: "high frequency" AND "spinal cord stimulation" = 1 (4 records found – 3 were duplicates of records already found, so were not retrieved)

A3: EAC additional search methods

A *de novo* literature search was undertaken by the EAC. The search aimed to identify evidence on HF10 therapy using the Senza spinal cord simulation system in patients undergoing spinal cord stimulation for chronic pain.

A strategy was developed for MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through assessment of the company's strategy, discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (<http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi>). The approach taken to search strategy development aimed to balance sensitivity and precision, reflecting the project resource and timelines.

The main structure of the strategy comprised 2 concepts:

- Spinal cord stimulation (SCS);
- HF10 therapy.

The concepts were combined as follows: spinal cord stimulation AND HF-10 therapy. The strategy also included 2 standalone lines which search on the device name and the pre-coordinated term *HFSCS*.

The strategy excluded animal studies using a standard algorithm. The search was limited to studies published in English as project timelines and resource precluded the translation of foreign language papers. Reflecting the timeframe of the existence of the company (as stated in the submission), searches were restricted to studies published from 2006 to date. The search was not restricted by study design.

The performance of the draft MEDLINE strategy was checked at development stage by testing successful retrieval of the 9 relevant studies identified in the submission (Section 7.3.1, Table 6: List of relevant published studies, Submission). The draft strategy successfully retrieved all 9 studies.

The final strategy for MEDLINE is shown in Figure A3.1.

Figure A3.1: EAC search strategy for Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

1	Spinal Cord Stimulation/ (566)
2	exp Spinal Cord/ and (electric stimulation therapy/ or Electric Stimulation/) (8845)
3	exp Spinal Cord/ and (stimulat\$ or electrostimulat\$).ti,ab,kf. (13725)
4	spinal cord\$.ti,ab,kf. and (electric stimulation therapy/ or Electric Stimulation/) (7636)
5	(spinal cord\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (5645)
6	(sc adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (1271)
7	scs.ti,ab,kf. (6444)
8	((spine or spines) adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (460)
9	(column\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (933)
10	(epidur\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (937)
11	or/1-10 (29319)
12	(hf10\$2 or hf-10\$2).ti,ab,kf. (199)
13	(high frequenc\$ or highfrequenc\$).ti,ab,kf. (79201)
14	(10 khz or 10khz or 10 kilohertz or 10kilohertz or 10 kilo-hertz or 10kilo-hertz or 10,000 hz or 10,000hz or 10000 hz or 10000hz or 10,000 hertz or 10,000hertz or 10000 hertz or 10000hertz).ti,ab,kf. (2046)
15	nevro\$2.ti,ab,kf,in. (83)
16	senza\$2.ti,ab,kf. (185)
17	or/12-16 (81368)
18	11 and 17 (629)
19	(hfscs or hf-scs).ti,ab,kf. (113)
20	senza\$2.ti,ab,kf. not senza\$2.oa. (14)
21	or/18-20 (734)
22	exp animals/ not humans/ (4417382)
23	21 not 22 (277)
24	limit 23 to (english language and yr="2006 -Current") (196)
25	remove duplicates from 24 (190)
Key to Ovid symbols and commands	
\$	Unlimited right-hand truncation symbol
\$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,in,oa.	Searches are restricted to the Title, Abstract, Keyword Heading Word, Institution, Other Abstract fields
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
or/1-10	Combines sets 1 to 10 using OR

yr="2006 -Current") Publication year 2006 to current

EAC additional searches: information resources

The final Ovid MEDLINE strategy was translated appropriately for the other information resources searched (shown in Table A3.1). The information resources included a range of databases containing both research published in the journal literature, conference abstracts and ongoing research. The EAC also conducted focused searches of a selection of additional websites informed by the list of external organisations identified on the NICE final scope document for the technology. The PubMed search was restricted to just those records not fully indexed in MEDLINE. In discussion with NICE it was decided that no hand-searches of specific conference proceedings was required.

Table A3.1: *EAC additional searches: databases and information resources searched*

Database / information resource	Interface / url
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	OvidSP
Embase	OvidSP
Cochrane Central Register of Controlled Trials	Cochrane Library / Wiley
Database of Abstracts of Reviews of Effect	Cochrane Library / Wiley
Health Technology Assessment Database	Cochrane Library / Wiley
Cochrane Database of Systematic Reviews	Cochrane Library / Wiley
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Science Citation Index Expanded (SCI-EXPANDED)	Web of Science
Conference Proceedings Citation Index- Science (CPCI-S)	Web of Science
Scopus	Scopus.com
Econlit	OvidSP
Cost-Effectiveness Analysis (CEA) Registry	https://research.tufts-nemc.org/cear4/
Clinicaltrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform	http://apps.who.int/trialsearch/
ISRCTN registry	http://www.isrctn.com/
NHS Economic Evaluation Database	Cochrane Library / Wiley
Euroscan	https://www.euroscan.org/
Association of Occupational Health Nurse Practitioners website	http://aohnp.co.uk/

Database / information resource	Interface / url
British Association of Spinal Surgeons website	http://www.spinesurgeons.ac.uk/
British Chiropractic Association website	https://chiropractic-uk.co.uk/
British Institute of Musculoskeletal Medicine website	http://www.bimm.org.uk/
British Orthopaedic Association website	http://www.boa.ac.uk/
Institute of Osteopathy website	http://www.osteopathy.org/
British Pain Society website	https://www.britishpainsociety.org/
British Society for Rheumatology website	https://www.rheumatology.org.uk/
British Society of Rehabilitation Medicine website	http://www.bsrm.org.uk/
Chartered Society of Physiotherapy website	http://www.csp.org.uk/
Royal College of Occupational Therapists website	https://www.rcot.co.uk/
Royal College of Nursing website	https://www.rcn.org.uk/
Royal College of Physicians website	https://www.rcplondon.ac.uk/
Royal College of Surgeons website	https://www.rcseng.ac.uk/
Society for Back Pain Research website	http://www.sbpr.info/
BackCare website	http://www.backcare.org.uk/
Fighting Back UK website	http://fightingbackuk.com/
Action on Pain website	http://www.action-on-pain.co.uk/
Pain Association Scotland website	http://www.painassociation.com/
Pain Concern website	http://painconcern.org.uk/
Pain Relief Foundation website	http://www.painrelieffoundation.org.uk/
Pain UK website	https://painuk.org/
Nevro website – Clinical Evidence webpage	http://www.nevro.com/English/Physicians/Clinical-Evidence/default.aspx

Results of the searches were downloaded and imported into EndNote reference management software. The records retrieved by the EAC search were deduplicated using several algorithms, both within-set and against the records retrieved by the re-run company's searches.

EAC additional searches: search results

The EAC searches database and website searches identified 1,446 records (Table A3.2). After deduplication, 637 records remained. Of the 637 records, 244 were identified as conference-related publication types from Embase and the Conference Proceedings Citation Index - Science database. Following discussion with NICE, it was agreed that conference-related publication types would be excluded from the EAC report, leaving 393 records for assessment.

Table A3.2: EAC additional searches: results

Database / information resource	Records identified
---------------------------------	--------------------

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)	190
Embase	393
Cochrane Central Register of Controlled Trials	63
Database of Abstracts of Reviews of Effect	0
Health Technology Assessment Database	0
Cochrane Database of Systematic Reviews	3
PubMed	101
Science Citation Index Expanded (SCI-EXPANDED)	245
Conference Proceedings Citation Index- Science (CPCI-S)	24
Scopus	250
Econlit	3
Cost-Effectiveness Analysis (CEA) Registry	0
Clinicaltrials.gov	66
WHO International Clinical Trials Registry Platform	91
ISRCTN Registry	16
NHS Economic Evaluation Database	0
Euroscan	1
Association of Occupational Health Nurse Practitioners website	0
British Association of Spinal Surgeons website	0
British Chiropractic Association website	0
British Institute of Musculoskeletal Medicine website	0
British Orthopaedic Association website	0
Institute of Osteopathy website	0
British Pain Society website	0
British Society for Rheumatology website	0
British Society of Rehabilitation Medicine website	0
Chartered Society of Physiotherapy website	0
Royal College of Occupational Therapists website	0
Royal College of Nursing website	0
Royal College of Physicians website	0
Royal College of Surgeons website	0
Society for Back Pain Research website	0
BackCare website	0
Fighting Back UK website	0
Action on Pain website	0
Pain Association Scotland website	0
Pain Concern website	0
Pain Relief Foundation website	0
Pain UK website	0
Nevro website – Clinical Evidence webpage	0
TOTAL	1446

TOTAL after deduplication (within-set and against results retrieved by the re-run company's searches)	637
TOTAL assessed after removal of conference-related publication types	393

EAC additional searches: full search strategies

A.1: Source: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Interface / URL: OvidSP

Database coverage dates: 1946 to current. Updated daily.

Search date: 13/06/17

Retrieved records: 190

Search strategy:

- 1 Spinal Cord Stimulation/ (566)
- 2 exp Spinal Cord/ and (electric stimulation therapy/ or Electric Stimulation/) (8845)
- 3 exp Spinal Cord/ and (stimulat\$ or electrostimulat\$).ti,ab,kf. (13725)
- 4 spinal cord\$.ti,ab,kf. and (electric stimulation therapy/ or Electric Stimulation/) (7636)
- 5 (spinal cord\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (5645)
- 6 (sc adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (1271)
- 7 scs.ti,ab,kf. (6444)
- 8 ((spine or spines) adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (460)
- 9 (column\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (933)
- 10 (epidur\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kf. (937)
- 11 or/1-10 (29319)
- 12 (hf10\$2 or hf-10\$2).ti,ab,kf. (199)
- 13 (high frequenc\$ or highfrequenc\$).ti,ab,kf. (79201)
- 14 (10 khz or 10khz or 10 kilohertz or 10kilohertz or 10 kilo-hertz or 10kilo-hertz or 10,000 hz or 10,000hz or 10000 hz or 10000hz or 10,000 hertz or 10,000hertz or 10000 hertz or 10000hertz).ti,ab,kf. (2046)
- 15 nevro\$2.ti,ab,kf,in. (83)
- 16 senza\$2.ti,ab,kf. (185)
- 17 or/12-16 (81368)
- 18 11 and 17 (629)
- 19 (hfscs or hf-scs).ti,ab,kf. (113)
- 20 senza\$2.ti,ab,kf. not senza\$2.oa. (14)
- 21 or/18-20 (734)
- 22 exp animals/ not humans/ (4417382)
- 23 21 not 22 (277)
- 24 limit 23 to (english language and yr="2006 -Current") (196)
- 25 remove duplicates from 24 (190)

A.2: Source: Embase

Interface / URL: OvidSP

Database coverage dates: 1974 to 2017 June 12

Search date: 13/06/17

Retrieved records: 393

Search strategy:

- 1 spinal cord stimulation/ (5250)
- 2 (spinal cord\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kw. (8114)
- 3 (sc adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kw. (1608)
- 4 scs.ti,ab,kw. (8858)
- 5 ((spine or spines) adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kw. (583)
- 6 (column\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kw. (1199)
- 7 (epidur\$ adj7 (stimulat\$ or electrostimulat\$)).ti,ab,kw. (1315)
- 8 or/1-7 (19513)
- 9 (HF10\$2 or HF-10\$2).ti,ab,kw. (387)
- 10 (high frequenc\$ or highfrequenc\$).ti,ab,kw. (94271)
- 11 (10 khz or 10khz or 10 kilohertz or 10kilohertz or 10 kilo-hertz or 10kilo-hertz or 10,000 hz or 10,000hz or 10000 hz or 10000hz or 10,000 hertz or 10,000hertz or 10000 hertz or 10000hertz).ti,ab,kw. (1926)
- 12 nevro\$2.ti,ab,kw,in,dm. (795)
- 13 or/9-12 (96819)
- 14 8 and 13 (514)
- 15 (hfscs or hf-scs).ti,ab,kw. (178)
- 16 senza\$2.ti,ab,kw,dv,dm,hw. (88)
- 17 or/14-16 (677)
- 18 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5663548)
- 19 17 not 18 (470)
- 20 limit 19 to (english language and yr="2006 -Current") (411)
- 21 remove duplicates from 20 (393)
- 22 (conference abstract or conference paper or conference proceeding or conference review).pt. (3323840)
- 23 21 and 22 (258)
- 24 21 not 23 (135)

A.3: Source: Database of Abstracts of Reviews of Effects

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Issue 2 of 4, April 2015

Search date: 13/06/17

Retrieved records: 0

Search strategy:

- #1 [mh ^"Spinal Cord Stimulation"] 36
- #2 [mh "Spinal Cord"] and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 132
- #3 [mh "Spinal Cord"] and (stimulat* or electrostimulat*) 236

#4 (spinal next cord*) and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 291

#5 ((spinal next cord*) near/7 (stimulat* or electrostimulat*)) 612

#6 (sc near/7 (stimulat* or electrostimulat*)) 402

#7 (scs) 585

#8 ((spine or spines) near/7 (stimulat* or electrostimulat*)) 116

#9 (column* near/7 (stimulat* or electrostimulat*)) 13

#10 (epidur* near/7 (stimulat* or electrostimulat*)) 140

#11 {or #1-#10} 1800

#12 (hf10* or hf-10*) 68

#13 (high next frequenc* or highfrequenc*) 4024

#14 ("10 khz" or 10khz or "10 kilohertz" or 10kilohertz or "10 kilo-hertz" or 10kilo-hertz or "10,000 hz" or 10,000hz or "10000 hz" or 10000hz or "10,000 hertz" or 10,000hertz or "10000 hertz" or 10000hertz) 52

#15 (nevro*) 598

#16 {or #12-#15} 4698

#17 #11 and #16 81

#18 (hfscs or hf-scs) 2

#19 (senza*) 38

#20 #17 or #18 or #19 109

#21 #20 Publication Year from 2006 to 2017 84

#22 #21 in Other Reviews 0

A.4: Source: Cochrane Central Register of Controlled Trials

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Issue 5 of 12, May

Search date: 13/06/17

Retrieved records: 63

Search strategy:

#1 [mh ^"Spinal Cord Stimulation"] 36

#2 [mh "Spinal Cord"] and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 132

#3 [mh "Spinal Cord"] and (stimulat* or electrostimulat*) 236

#4 (spinal next cord*) and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 291

#5 ((spinal next cord*) near/7 (stimulat* or electrostimulat*)) 612

#6 (sc near/7 (stimulat* or electrostimulat*)) 402

#7 (scs) 585

#8 ((spine or spines) near/7 (stimulat* or electrostimulat*)) 116

#9 (column* near/7 (stimulat* or electrostimulat*)) 13

#10 (epidur* near/7 (stimulat* or electrostimulat*)) 140

#11 {or #1-#10} 1800

#12 (hf10* or hf-10*) 68

#13 (high next frequenc* or highfrequenc*) 4024

#14 ("10 khz" or 10khz or "10 kilohertz" or 10kilohertz or "10 kilo-hertz" or 10kilo-
hertz or "10,000 hz" or 10,000hz or "10000 hz" or 10000hz or "10,000 hertz" or
10,000hertz or "10000 hertz" or 10000hertz) 52

#15 (nevro*) 598

#16 {or #12-#15} 4698

#17 #11 and #16 81

#18 (hfscs or hf-scs) 2

#19 (senza*) 38

#20 #17 or #18 or #19 109

#21 #20 Publication Year from 2006 to 2017 84

#22 #21 in Other Reviews 0

#23 #21 in Trials 63

A.5: Source: Health Technology Assessment Database

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Issue 4 of 4, October 2016

Search date: 13/07/16

Retrieved records: 0

Search strategy:

#1 [mh ^"Spinal Cord Stimulation"] 36

#2 [mh "Spinal Cord"] and ([mh ^"electric stimulation therapy"] or [mh ^"Electric
Stimulation"]) 132

#3 [mh "Spinal Cord"] and (stimulat* or electrostimulat*) 236

#4 (spinal next cord*) and ([mh ^"electric stimulation therapy"] or [mh ^"Electric
Stimulation"]) 291

#5 ((spinal next cord*) near/7 (stimulat* or electrostimulat*)) 612

#6 (sc near/7 (stimulat* or electrostimulat*)) 402

#7 (scs) 585

#8 ((spine or spines) near/7 (stimulat* or electrostimulat*)) 116

#9 (column* near/7 (stimulat* or electrostimulat*)) 13

#10 (epidur* near/7 (stimulat* or electrostimulat*)) 140

#11 {or #1-#10} 1800

#12 (hf10* or hf-10*) 68

#13 (high next frequenc* or highfrequenc*) 4024

#14 ("10 khz" or 10khz or "10 kilohertz" or 10kilohertz or "10 kilo-hertz" or 10kilo-
hertz or "10,000 hz" or 10,000hz or "10000 hz" or 10000hz or "10,000 hertz" or
10,000hertz or "10000 hertz" or 10000hertz) 52

#15 (nevro*) 598

#16 {or #12-#15} 4698

#17 #11 and #16 81

#18 (hfscs or hf-scs) 2

#19 (senza*) 38

#20 #17 or #18 or #19 109

#21 #20 Publication Year from 2006 to 2017 84

#22 #21 in Other Reviews 0

#23 #21 in Trials 63
#24 #21 in Technology Assessments 0

A.6: Source: NHS Economic Evaluation Database

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Issue 2 of 4, April 2015

Search date: 13/07/16

Retrieved records: 0

Search strategy:

#1 [mh ^"Spinal Cord Stimulation"] 36
#2 [mh "Spinal Cord"] and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 132
#3 [mh "Spinal Cord"] and (stimulat* or electrostimulat*) 236
#4 (spinal next cord*) and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 291
#5 ((spinal next cord*) near/7 (stimulat* or electrostimulat*)) 612
#6 (sc near/7 (stimulat* or electrostimulat*)) 402
#7 (scs) 585
#8 ((spine or spines) near/7 (stimulat* or electrostimulat*)) 116
#9 (column* near/7 (stimulat* or electrostimulat*)) 13
#10 (epidur* near/7 (stimulat* or electrostimulat*)) 140
#11 {or #1-#10} 1800
#12 (hf10* or hf-10*) 68
#13 (high next frequenc* or highfrequenc*) 4024
#14 ("10 khz" or 10khz or "10 kilohertz" or 10kilohertz or "10 kilo-hertz" or 10kilo-hertz or "10,000 hz" or 10,000hz or "10000 hz" or 10000hz or "10,000 hertz" or 10,000hertz or "10000 hertz" or 10000hertz) 52
#15 (nevro*) 598
#16 {or #12-#15} 4698
#17 #11 and #16 81
#18 (hfscs or hf-scs) 2
#19 (senza*) 38
#20 #17 or #18 or #19 109
#21 #20 Publication Year from 2006 to 2017 84
#22 #21 in Other Reviews 0
#23 #21 in Trials 63
#24 #21 in Technology Assessments 0
#25 #21 in Economic Evaluations 0

A.7: Source: Cochrane Database of Systematic Reviews

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Issue 6 of 12, June 2017

Search date: 13/06/17

Retrieved records: 3

Search strategy:

- #1 [mh ^"Spinal Cord Stimulation"] 36
- #2 [mh "Spinal Cord"] and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 132
- #3 [mh "Spinal Cord"] and (stimulat* or electrostimulat*):ti,ab,kw 236
- #4 (spinal next cord*):ti,ab,kw and ([mh ^"electric stimulation therapy"] or [mh ^"Electric Stimulation"]) 269
- #5 ((spinal next cord*) near/7 (stimulat* or electrostimulat*)):ti,ab,kw 573
- #6 (sc near/7 (stimulat* or electrostimulat*)):ti,ab,kw 362
- #7 (scs):ti,ab,kw 307
- #8 ((spine or spines) near/7 (stimulat* or electrostimulat*)):ti,ab,kw 94
- #9 (column* near/7 (stimulat* or electrostimulat*)):ti,ab,kw 9
- #10 (epidur* near/7 (stimulat* or electrostimulat*)):ti,ab,kw 120
- #11 {or #1-#10} 1417
- #12 (hf10* or hf-10*):ti,ab,kw 4177
- #13 (high next frequenc* or highfrequenc*):ti,ab,kw 3643
- #14 ("10 khz" or 10khz or "10 kilohertz" or 10kilohertz or "10 kilo-hertz" or 10kilo-hertz or "10,000 hz" or 10,000hz or "10000 hz" or 10000hz or "10,000 hertz" or 10,000hertz or "10000 hertz" or 10000hertz):ti,ab,kw 47
- #15 (nevro*):ti,ab,kw 55
- #16 {or #12-#15} 7326
- #17 #11 and #16 69
- #18 (hfscs or hf-scs):ti,ab,kw 2
- #19 (senza*) 38
- #20 #17 or #18 or #19 97
- #21 #20 Publication Year from 2006 to 2017 74
- #22 #21 in Cochrane Reviews (Reviews and Protocols) 3

A.8: Source: Science Citation Index Expanded (SCI-EXPANDED)

Interface / URL: Web of Science

Database coverage dates: 1900 - present

Search date: 13/06/17

Retrieved records: 245

Search strategy:

All search lines - Indexes=SCI-EXPANDED

19 245 (#18) AND LANGUAGE: (English) Timespan=2006-2017

18 348 #16 not #17

17 2,468,452 TI=("rat" or "rats" or "rodent" or "rodents" or "mouse" or "mice" or "murine" or "hamster" or "hamsters" or "gerbil" or "gerbils" or "animal" or "animals" or "dogs" or "dog" or "canine" or "pig" or "pigs" or "piglet" or "piglets" or "cats" or "bovine" or "cow" or "cows" or "cattle" or "sheep" or "ewe" or "ewes" or "horse" or "horses" or "equine" or "ovine" or "porcine" or "monkey" or "monkeys" or "primate" or

"primates" or "rhesus macaque" or "rhesus macaques" or "rabbit" or "rabbits") NOT
TS=(human* or "women" or "woman" or "man" or "men" or "child" or "children" or
adolescen* or teenager* or "people" or boy or boys or girl or girls)

16 412 #15 OR #14 OR #13

15 36 TS=(senza*)

14 91 TS= ("hfscs" or "hf-scs")

13 310 #12 AND #7

12 149,553 #11 OR #10 OR #9 OR #8

11 239 TS=(nevro*)

10 5,906 TS=("10 khz" or "10khz" or "10 kilohertz" or "10kilohertz" or "10 kilo-
hertz" or "10kilo-hertz" or "10,000 hz" or "10,000hz" or "10000 hz" or "10000hz" or
"10,000 hertz" or "10,000hertz" or "10000 hertz" or "10000hertz")

9 143,829 TS=("high frequenc*" or highfrequenc*)

8 259 TS=(hf10* or hf-10*)

7 17,942 #6 OR #5 OR #4 OR #3 OR #2 OR #1

6 853 TS=(epidur* near/7 (stimulat* or electrostimulat*))

5 969 TS=(column* near/7 (stimulat* or electrostimulat*))

4 402 TS=(("spine" or "spines") near/7 (stimulat* or electrostimulat*))

3 10,795 TS=("scs")

2 1,019 TS= ("sc" near/7 (stimulat* or electrostimulat*))

1 5,723 TS=("spinal cord*" near/7 (stimulat* or electrostimulat*))

A.9: Source: Conference Proceedings Citation Index- Science (CPCI-S)

Interface / URL: Web of Science

Database coverage dates: 1990 - present

Search date: 13/9/17

Retrieved records: 24

Search strategy:

All search lines - Indexes=CPCI-S

19 24 (#18) AND LANGUAGE: (English) Timespan=2006-2017

18 37 #16 not #17

17 222,987 TI=("rat" or "rats" or "rodent" or "rodents" or "mouse" or "mice" or "murine" or "hamster" or "hamsters" or "gerbil" or "gerbils" or "animal" or "animals" or "dogs" or "dog" or "canine" or "pig" or "pigs" or "piglet" or "piglets" or "cats" or "bovine" or "cow" or "cows" or "cattle" or "sheep" or "ewe" or "ewes" or "horse" or "horses" or "equine" or "ovine" or "porcine" or "monkey" or "monkeys" or "primate" or "primates" or "rhesus macaque" or "rhesus macaques" or "rabbit" or "rabbits") NOT TS=(human* or "women" or "woman" or "man" or "men" or "child" or "children" or adolescen* or teenager* or "people" or boy or boys or girl or girls)

16 42 #15 OR #14 OR #13

15 4 TS=(senza*)

14 3 TS= ("hfscs" or "hf-scs")

13 38 #12 AND #7

12 50,852 #11 OR #10 OR #9 OR #8

11 10 TS=(nevro*)

10 3,023 TS=("10 khz" or "10khz" or "10 kilohertz" or "10kilohertz" or "10 kilo-hertz" or "10kilo-hertz" or "10,000 hz" or "10,000hz" or "10000 hz" or "10000hz" or "10,000 hertz" or "10,000hertz" or "10000 hertz" or "10000hertz")

9 48,039 TS=("high frequenc*" or highfrequenc*)

8 42 TS=(hf10* or hf-10*)

7 2,590 #6 OR #5 OR #4 OR #3 OR #2 OR #1

6 118 TS=(epidur* near/7 (stimulat* or electrostimulat*))

5 74 TS=(column* near/7 (stimulat* or electrostimulat*))

4 32 TS=(("spine" or "spines") near/7 (stimulat* or electrostimulat*))

3 1,815 TS=("scs")

2 63 TS= ("sc" near/7 (stimulat* or electrostimulat*))

1 694 TS=("spinal cord*" near/7 (stimulat* or electrostimulat*))

A.10: Source: PubMed

Interface / URL: <https://www.ncbi.nlm.nih.gov/pubmed/>

Database coverage dates: 1940s to current. Updated daily.

Search date: 14/06/17

Retrieved records: 101

Search strategy:

#27 Search (#25 NOT #26) 101
#26 Search medline[sb] 24075874
#25 Search (#21 NOT #22) Filters: Publication date from 2006/01/01 to 2017/12/31; English 243
#24 Search (#21 NOT #22) Filters: English 323
#23 Search (#21 NOT #22) 352
#22 Search (animals[mh] NOT humans[mh:noexp]) 4336883
#21 Search (#18 OR #19 OR #20) 894
#20 Search senza*[tiab] NOT hasnonenglishabstract 17
#19 Search (hfscs[tiab] OR hf-scs[tiab]) 96
#18 Search (#11 AND #17) 802
#17 Search (#12 OR #13 OR #14 OR #15 OR #16) 81554
#16 Search senza*[tiab] 223
#15 Search (nevro*[tiab] OR nevro*[ad]) 820
#14 Search (10 khz[tiab] OR 10khz[tiab] OR kilohertz[tiab] OR 10kilohertz[tiab] OR hertz[tiab] OR 10,000 hz[tiab] OR 10 000 hz[tiab] OR 10000 hz[tiab] OR 10000hz[tiab] OR 000hertz[tiab] OR 10000hertz[tiab]) 3601
#13 Search (high frequenc*[tiab] OR highfrequenc*[tiab]) 77216
#12 Search ((hf10*[tiab] OR hf-10*[tiab])) 142
#11 Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 44074
#10 Search (epidur*[tiab] AND (stimulat*[tiab] OR electrostimulat*[tiab])) 2027
#9 Search (column*[tiab] AND (stimulat*[tiab] OR electrostimulat*[tiab])) 7425
#8 Search ((spine[tiab] OR spines[tiab]) AND (stimulat*[tiab] OR electrostimulat*[tiab])) 2917
#7 Search scs[tiab] 6175
#6 Search (sc[tiab] AND (stimulat*[tiab] OR electrostimulat*[tiab])) 4453
#5 Search (spinal cord*[tiab] AND (stimulat*[tiab] OR electrostimulat*[tiab])) 16408
#4 Search spinal cord*[tiab] AND (electric stimulation therapy [mh:noexp] OR Electric Stimulation [mh:noexp]) 7501
#3 Search Spinal Cord [mh] AND (stimulat*[tiab] OR electrostimulat*[tiab]) 13489
#2 Search Spinal Cord [mh] AND (electric stimulation therapy [mh:noexp] OR Electric Stimulation [mh:noexp]) 8692

A.11: Source: Scopus

Interface / URL: scopus.com

Database coverage dates: Information not found

Search date: 15/06/17

Retrieved records: 250

Search strategy:

22 ((((((TITLE-ABS-KEY("spinal cord*" W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(sc W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(scs)) OR (TITLE-ABS-KEY((spine OR spines) W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(column* W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(epidur* W/7 (stimulat* OR electrostimulat*)))) AND ((TITLE-ABS-KEY(hf10* OR hf-10*)) OR (TITLE-ABS-KEY("high frequenc*" OR highfrequenc*)) OR (TITLE-ABS-KEY("10 khz" OR 10khz OR kilohertz OR 10kilohertz OR hertz OR "10,000 hz" OR "10,000hz" OR "10000 hz" OR 10000hz OR "10,000hertz" OR 10000hertz)) OR (TITLE-ABS-KEY(nevro*) OR MANUFACTURER(nevro*) OR AFFIL(nevro*)) OR (TITLE-ABS(senza*))) OR (TITLE-ABS-KEY(hfscs OR hf-scs)) OR (KEY(senza*) OR TRADENAME(senza*))) AND (LANGUAGE(english)) AND (PUBYEAR > 2005)) AND NOT ((KEY(nonhuman)) AND NOT (KEY(human OR humans))) 250 document results

21 (KEY(nonhuman)) AND NOT (KEY(human OR humans))
3,290,794 document results

20 ((((((TITLE-ABS-KEY("spinal cord*" W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(sc W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(scs)) OR (TITLE-ABS-KEY((spine OR spines) W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(column* W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(epidur* W/7 (stimulat* OR electrostimulat*)))) AND ((TITLE-ABS-KEY(hf10* OR hf-10*)) OR (TITLE-ABS-KEY("high frequenc*" OR highfrequenc*)) OR (TITLE-ABS-KEY("10 khz" OR 10khz OR kilohertz OR 10kilohertz OR hertz OR "10,000 hz" OR "10,000hz" OR "10000 hz" OR 10000hz OR "10,000hertz" OR 10000hertz)) OR (TITLE-ABS-KEY(nevro*) OR MANUFACTURER(nevro*) OR AFFIL(nevro*)) OR (TITLE-ABS(senza*))) OR (TITLE-ABS-KEY(hfscs OR hf-scs)) OR (KEY(senza*) OR TRADENAME(senza*))) AND (LANGUAGE(english)) AND (PUBYEAR > 2005) 345 document results

19 PUBYEAR > 2005 28,920,493 document results

18 LANGUAGE(english) 57,672,763 document results

17 (((TITLE-ABS-KEY("spinal cord*" W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY(sc W/7 (stimulat* OR

electrostimulat*)) OR (TITLE-ABS-KEY (scs)) OR (TITLE-ABS-KEY ((spine OR spines) W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (column* W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (epidur* W/7 (stimulat* OR electrostimulat*))) AND ((TITLE-ABS-KEY (hf10* OR hf-10*)) OR (TITLE-ABS-KEY ("high frequenc*" OR highfrequenc*)) OR (TITLE-ABS-KEY ("10 khz" OR 10khz OR kilohertz OR 10kilohertz OR hertz OR "10,000 hz" OR "10,000hz" OR "10000 hz" OR 10000hz OR "10,000hertz" OR 10000hertz)) OR (TITLE-ABS-KEY (nevro*) OR MANUFACTURER (nevro*) OR AFFIL (nevro*)) OR (TITLE-ABS (senza*))) OR (TITLE-ABS-KEY (hfscs OR hf-scs)) OR (KEY (senza*) OR TRADENAME (senza*)) 544 document results

16 KEY (senza*) OR TRADENAME (senza*) 11 document results

15 TITLE-ABS-KEY (hfscs OR hf-scs) 101 document results

14 ((TITLE-ABS-KEY ("spinal cord*" W/7 (stimulat* OR electrostimulat*)))) OR (TITLE-ABS-KEY (sc W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (scs)) OR (TITLE-ABS-KEY ((spine OR spines) W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (column* W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (epidur* W/7 (stimulat* OR electrostimulat*)))) AND ((TITLE-ABS-KEY (hf10* OR hf-10*)) OR (TITLE-ABS-KEY ("high frequenc*" OR highfrequenc*)) OR (TITLE-ABS-KEY ("10 khz" OR 10khz OR kilohertz OR 10kilohertz OR hertz OR "10,000 hz" OR "10,000hz" OR "10000 hz" OR 10000hz OR "10,000hertz" OR 10000hertz)) OR (TITLE-ABS-KEY (nevro*) OR MANUFACTURER (nevro*) OR AFFIL (nevro*)) OR (TITLE-ABS (senza*))) 453 document results

13 (TITLE-ABS-KEY (hf10* OR hf-10*)) OR (TITLE-ABS-KEY ("high frequenc*" OR highfrequenc*)) OR (TITLE-ABS-KEY ("10 khz" OR 10khz OR kilohertz OR 10kilohertz OR hertz OR "10,000 hz" OR "10,000hz" OR "10000 hz" OR 10000hz OR "10,000hertz" OR 10000hertz)) OR (TITLE-ABS-KEY (nevro*) OR MANUFACTURER (nevro*) OR AFFIL (nevro*)) OR (TITLE-ABS (senza*)) 354,851 document results

12 TITLE-ABS (senza*) 1,474 document results

11 TITLE-ABS-KEY (nevro*) OR MANUFACTURER (nevro*) OR AFFIL (nevro*) 5,478 document results

10 TITLE-ABS-KEY ("10 khz" OR 10khz OR kilohertz OR 10kilohertz OR hertz OR "10,000 hz" OR "10,000hz" OR "10000 hz" OR 10000hz OR "10,000hertz" OR 10000hertz) 29,611 document results

9 TITLE-ABS-KEY ("high frequenc*" OR highfrequenc*) 320,472 document results

8 TITLE-ABS-KEY (hf10* OR hf-10*) 308 document results

- 7 (TITLE-ABS-KEY ("spinal cord*" W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (sc W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (scs)) OR (TITLE-ABS-KEY ((spine OR spines) W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (column* W/7 (stimulat* OR electrostimulat*))) OR (TITLE-ABS-KEY (epidur* W/7 (stimulat* OR electrostimulat*))) 28,239 document results
- 6 TITLE-ABS-KEY (epidur* W/7 (stimulat* OR electrostimulat*)) 1,216 document results
- 5 TITLE-ABS-KEY (column* W/7 (stimulat* OR electrostimulat*)) 1,483 document results
- 4 TITLE-ABS-KEY ((spine OR spines) W/7 (stimulat* OR electrostimulat*)) 578 document results
- 3 TITLE-ABS-KEY (scs) 17,459 document results
- 2 TITLE-ABS-KEY (sc W/7 (stimulat* OR electrostimulat*)) 2,287 document results
- 1 TITLE-ABS-KEY ("spinal cord*" W/7 (stimulat* OR electrostimulat*)) 8,655 document results

Note: sets were combined in lines 7, 13, 14, 17, 20, 22 using line numbers in the Scopus Advanced interface. For example, line 7 above is how the Scopus interface represents a search of #1 OR #2 OR #3 OR #4 OR #5 OR #6.

A.12: Source: Econlit

Interface / URL: OvidSP

Database coverage dates: 1886 to May 2017

Search date: 15/06/17

Retrieved records: 3

Search strategy:

- 1 (spinal cord\$ adj7 (stimulat\$ or electrostimulat\$)).af. (0)
- 2 (sc adj7 (stimulat\$ or electrostimulat\$)).af. (1)
- 3 scs.af. (77)
- 4 ((spine or spines) adj7 (stimulat\$ or electrostimulat\$)).af. (0)
- 5 (column\$ adj7 (stimulat\$ or electrostimulat\$)).af. (1)
- 6 (epidur\$ adj7 (stimulat\$ or electrostimulat\$)).af. (0)
- 7 or/1-6 (79)
- 8 (hf10\$2 or hf-10\$2).af. (0)
- 9 (high frequenc\$ or highfrequenc\$).af. (2689)
- 10 (10 khz or 10khz or 10 kilohertz or 10kilohertz or 10 kilo-hertz or 10kilo-hertz or 10,000 hz or 10,000hz or 10000 hz or 10000hz or 10,000 hertz or 10,000hertz or 10000 hertz or 10000hertz).af. (0)
- 11 nevro\$2.af. (0)

- 12 or/8-11 (2689)
- 13 7 and 12 (0)
- 14 (hfscs or hf-scs).af. (0)
- 15 senza\$2.af. (36)
- 16 or/13-15 (36)
- 17 limit 16 to (yr="2006 -Current" and english) (3)

A.13: Source: Cost-Effectiveness Analysis (CEA) Registry

Interface / URL: <https://research.tufts-nemc.org/cear4/>

Database coverage dates: Information not found.

Search date: 15/06/17

Retrieved records: 0

Search strategy:

Freely available search functionality in CEA Registry is very basic – only single term search supported. Boolean operators required to search for necessary concepts are not available. There is no exporting functionality. As a result:

- The following 32 searches were carried out separately, using the basic interface;
- Returned results were assessed online by the information specialist for relevance to Senza – results which were definitely not relevant were excluded;
- Remaining results were only retrieved if not duplicates of records already retrieved via another source.

1. hf10 = 0 (3 results returned, 1 relevant – but already retrieved via MEDLINE)
2. hf10tm = 0 results returned
3. hf-10 = 0 results returned
4. hf-10tm = 0 results returned
5. hf 10 = 0 (5 results returned, 0 selected as relevant)
6. hf 10tm = 0 results returned
7. high frequency = 0 results returned
8. high-frequency = 0 (1 result returned, 1 relevant – but already retrieved via MEDLINE)
9. highfrequency = 0 results returned
10. khz = 0 (1 result returned, 1 relevant – but already retrieved via MEDLINE)
11. kilohertz = 0 (1 results returned, 0 selected)
12. kilo-hertz = 0 results returned
13. hertz = 0 (2 results returned, 0 selected)
14. hz = 0 (17 results returned, 1 relevant – but already retrieved via MEDLINE)
15. 10-khz = 0 results returned
16. 10-kilohertz = 0 results returned
17. 10-kilo-hertz = 0 results returned
18. 10khz = 0 results returned
19. 10kilohertz = 0 results returned
20. 10kilo-hertz = 0 results returned

21. 10,000hz = 0 results returned
22. 10 000hz = 0 results returned
23. 10000hz = 0 results returned
24. 10,000hertz = 0 results returned
25. 10 000hertz = 0 results returned
26. 10000hertz = 0 results returned
27. nevro = 0 results returned
28. nevrotm = 0 results returned
29. senza = 0 results returned
30. senzاتم = 0 results returned
31. hfscs = 0 results returned
32. hf-scs = 0 results returned

A.14: Source: ClinicalTrials.gov

Interface / URL: <https://clinicaltrials.gov/ct2/home>

Database coverage dates: Information not found.

Search date: 15/06/17

Retrieved records: 66

Search strategy:

The following 3 searches were conducted separately in the Expert interface. Results were downloaded separately.

1. (hf10 OR hf-10 OR hf10tm OR hf-10tm OR nevro OR nevrotm OR senza OR senzاتم OR hfscs OR hf-scs) = 15 records

2. ("spinal cord" OR "spinal cords" OR sc OR spine OR spines OR column OR columns OR epidural) AND (stimulation OR stimulations OR stimulate OR stimulates OR stimulatory OR electrostimulation OR electrostimulations OR electrostimulate OR electrostimulates OR electrostimulatory) AND ("high frequency" OR "high frequencies" OR highfrequency OR highfrequencies OR "10 khz" OR 10khz OR "10 kilohertz" OR 10kilohertz OR "10 kilo-hertz" OR 10kilo-hertz OR "10,000 hz" OR "10 000 hz" OR 10,000hz OR "10 000hz" OR "10000 hz" OR 10000hz OR "10,000 hertz" OR "10 000 hertz" OR 10,000hertz OR "10 000hertz" OR "10000 hertz" OR 10000hertz) = 36 records

3. scs AND ("high frequency" OR "high frequencies" OR highfrequency OR highfrequencies OR "10 khz" OR 10khz OR "10 kilohertz" OR 10kilohertz OR "10 kilo-hertz" OR 10kilo-hertz OR "10,000 hz" OR "10 000 hz" OR 10,000hz OR "10 000hz" OR "10000 hz" OR 10000hz OR "10,000 hertz" OR "10 000 hertz" OR 10,000hertz OR "10 000hertz" OR "10000 hertz" OR 10000hertz) = 15 records

A.15: Source: WHO International Clinical Trials Registry Platform (ICTRP)

Interface / URL: <http://apps.who.int/trialsearch/Default.aspx>

Database coverage dates: Information not found.

Search date: 16/06/17

Retrieved records: 91

Search strategy:

The following 4 searches were carried out separately, using the search interface at: <http://apps.who.int/trialsearch/Default.aspx>. Results were downloaded separately.

1. hf10 OR hf-10 OF hf 10 OR hf10tm OR hf-10tm OR hf 10tm OR nevro OR nevrotm OR senza OR senzاتم OR hfscs OR hf-scs OR hf scs OR highfrequency OR highfrequencies = 31 (32 records for 31 trials found)

2. 10 khz OR 10-khz OR 10khz OR 10 kilohertz OR 10-kilohertz OR 10kilohertz OR 10 kilo-hertz OR 10-kilo-hertz OR 10kilo-hertz OR 10,000 hz OR 10,000-hz OR 10 000 hz OR 10 000-hz OR 10,000hz OR 10 000hz OR 10000 hz OR 10000-hz OR 10000hz OR 10,000 hertz OR 10,000-hertz OR 10 000 hertz OR 10 000-hertz OR 10,000hertz OR 10 000hertz OR 10000 hertz OR 10000-hertz OR 10000hertz = 11 (11 records for 11 trials found)

3. spinal cord* AND stimulat* AND high frequenc* OR spinal cord* AND electrostimulat* AND high frequenc* OR sc AND stimulat* AND high frequenc* OR sc AND electrostimulat* AND high frequenc* OR spine AND stimulat* AND high frequenc* OR spine AND electrostimulat* AND high frequenc* OR spines AND stimulat* AND high frequenc* OR spines AND electrostimulat* AND high frequenc* OR column* AND stimulat* AND high frequenc* OR column* AND electrostimulat* AND high frequenc* OR epidur* AND stimulat* AND high frequenc* OR epidur* AND electrostimulat* AND high frequenc* = 34 (34 records for 34 trials found)

4. scs AND high frequenc* = 15 (15 records for 15 trials found)

A.16: Source: ISRCTN Registry

Interface / URL: <https://www.isrctn.com/>

Database coverage dates: Information not found.

Search date: 16/06/17

Retrieved records: 16

Search strategy:

The following 2 searches were carried out separately, using the homepage search interface. Results were downloaded separately.

1. hf10 OR hf-10 OR hf10tm OR hf-10tm OR nevro OR nevrotm OR senza OR senzاتم OR hfscs OR hf-scs OR highfrequency OR highfrequencies OR "10 khz" OR 10khz OR "10 kilohertz" OR 10kilohertz OR "10 kilo-hertz" OR 10kilo-hertz OR "10,000 hz" OR "10 000 hz" OR 10,000hz OR "10 000hz" OR "10000 hz" OR 10000hz OR "10,000 hertz" OR "10 000 hertz" OR 10,000hertz OR "10 000hertz" OR "10000 hertz" OR 10000hertz = 10 records

2. ("spinal cord" OR "spinal cords" OR sc OR scs OR spine OR spines OR column OR columns OR epidural) AND ("high frequency" OR "high frequencies") = 6 (9 records were returned, but 3 records were excluded as duplicates for records found in search 1)

A.17: Source: Euroscan

Interface / URL: <https://www.euroscan.org/>

Database coverage dates: Information not found.

Search date: 16/06/17

Retrieved records: 1

Search strategy:

The following searches were carried out separately, using the homepage search interface. Results were assessed online by the information specialist for relevance. Only search results returned under the headings 'Devices', 'Procedures' or 'Other' were assessed. Only results judged to be potentially relevant and which were not duplicates of results already found were retrieved.

1. hf10 OR "hf-10" OR hf10tm OR "hf-10tm" OR nevro OR nevrotm OR senza OR senzاتم OR hfscs OR "hf-scs" OR highfrequency OR highfrequencies OR "10 khz" OR 10khz OR "10 kilohertz" OR 10kilohertz OR "10 kilo-hertz" OR "10kilo-hertz" OR "10,000 hz" OR "10 000 hz" OR "10,000hz" OR "10 000hz" OR "10000 hz" OR 10000hz OR "10,000 hertz" OR "10 000 hertz" OR "10,000hertz" OR "10 000hertz" OR "10000 hertz" OR 10000hertz = 1 (7 results returned and assessed; 6 excluded as irrelevant)

2. ("spinal cord" OR "spinal cords" OR sc OR scs OR spine OR spines OR column* OR epidur*) AND ("high frequency" OR "high frequencies") = 0 (5 results returned and assessed; 4 excluded as irrelevant, 1 excluded as duplicate of record retrieved in search 1)

A.18: Source: Association of Occupational Health Nurse Practitioners website

Interface / URL: <http://aohnp.co.uk/>

Database coverage dates: Information not found.

Search date: 16/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<http://aohnp.co.uk/>

Searched Google using: SenzaTM site:<http://aohnp.co.uk/>

0 results returned

A.19: Source: British Association of Spinal Surgeons website

Interface / URL: <http://www.spinesurgeons.ac.uk/>

Database coverage dates: Information not found.

Search date: 16/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

0 results returned

Searched Google using: Senza site:<http://www.spinesurgeons.ac.uk/>

1 result returned (reference to a registry record already retrieved); 0 retrieved

Searched Google using: SenzaTM site:<http://www.spinesurgeons.ac.uk/>

0 results returned

A.20: Source: British Chiropractic Association website

Interface / URL: <https://chiropractic-uk.co.uk/>

Database coverage dates: Information not found.

Search date: 16/06/17

Retrieved records:

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<https://chiropractic-uk.co.uk/>

Searched Google using: SenzaTM site: <https://chiropractic-uk.co.uk/>

0 results returned

A.21: Source: British Institute of Musculoskeletal Medicine website

Interface / URL: <http://www.bimm.org.uk/>

Database coverage dates: Site not available on date of search

Search date: 16/06/17; 29/06/17

Retrieved records: 0

Search strategy:

Site not searched. Unable to access site at the above URL on above search dates – message “This site can’t be reached”. Unable to find an alternative URL.

A.22: Source: British Orthopaedic Association website

Interface / URL: <http://www.boa.ac.uk/>
Database coverage dates: Information not found.
Search date: 16/06/17
Retrieved records: 0
Search strategy:

Site wide search: Senza
Site wide search: SenzaTM

Searched Google using: Senza site:<http://www.boa.ac.uk/>
Searched Google using: SenzaTM site:<http://www.boa.ac.uk/>

0 results returned

A.23: Source: Institute of Osteopathy website

Interface / URL: <http://www.osteopathy.org/>
Database coverage dates: Information not found.
Search date: 16/06/17
Retrieved records: 0
Search strategy:

Site wide search: Senza
Site wide search: SenzaTM

Searched Google using: Senza site:<http://www.osteopathy.org/>
Searched Google using: SenzaTM site:<http://www.osteopathy.org/>

0 results returned

A.24: Source: British Pain Society website

Interface / URL: <https://www.britishpainsociety.org/>
Database coverage dates: Information not found.
Search date: 16/06/17
Retrieved records: 0
Search strategy:

Site wide search: Senza
Site wide search: SenzaTM

Searched Google using: Senza site:<https://www.britishpainsociety.org/>

2 returned results, both advertisements in Pain News; 0 records retrieved

Searched Google using: SenzaTM site:<https://www.britishpainsociety.org/>

0 returned results

A.25: Source: British Society for Rheumatology website

Interface / URL: <https://www.rheumatology.org.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<https://www.rheumatology.org.uk/>

Searched Google using: SenzaTM site:<https://www.rheumatology.org.uk/>

0 returned results

A.26: Source: British Society of Rehabilitation Medicine website

Interface / URL: <http://www.bsrm.org.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza = 0 (2 results returned, neither relevant, 0 retrieved)

Site wide search: SenzaTM = 0 (2 results returned, neither relevant, 0 retrieved)

Searched Google using: Senza site:<http://www.bsrm.org.uk/>

Searched Google using: SenzaTM site:<http://www.bsrm.org.uk/>

0 returned results

A.27: Source: Chartered Society of Physiotherapy website

Interface / URL: <http://www.csp.org.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<http://www.csp.org.uk/>

1 returned result – pdf of NICE TA159 Guidance Executive which refers to ISRCTN33292457 – latter retrieved previously. 0 records retrieved.

Searched Google using: SenzaTM site:<http://www.csp.org.uk/>

0 returned results

A.28: Source: Royal College of Occupational Therapists website

Interface / URL: <https://www.rcot.co.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<https://www.rcot.co.uk/>

Searched Google using: SenzaTM site:<https://www.rcot.co.uk/>

0 returned results

A.29: Source: Royal College of Nursing website

Interface / URL: <https://www.rcn.org.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<https://www.rcn.org.uk/>

Searched Google using: SenzaTM site:<https://www.rcn.org.uk/>

0 returned results

A.30: Source: Royal College of Physicians website

Interface / URL: <https://www.rcplondon.ac.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<https://www.rcplondon.ac.uk/>

Searched Google using: SenzaTM site:<https://www.rcplondon.ac.uk/>

0 returned results

A.31: Source: Royal College of Surgeons website

Interface / URL: <https://www.rcseng.ac.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<https://www.rcseng.ac.uk/>

Searched Google using: SenzaTM site:<https://www.rcseng.ac.uk/.uk/>

0 returned results

A.32: Source: Society for Back Pain Research website

Interface / URL: <http://www.sbpr.info/>

Database coverage dates: not known – unable to access website

Search date: 19/06/17

Retrieved records: 0

Search strategy:

URL for website sourced via: <http://www.ukssb.com/pages/Societies/Society-for-Back-Pain-Research.html>. URL does not lead to a website on dates of search (16/06/17 and 19/06/17), therefore unable to search via site. Unable to find an alternative URL.

A.33: Source: BackCare website

Interface / URL: <http://www.backcare.org.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records:

Search strategy: 0

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<http://www.backcare.org.uk/>

Searched Google using: SenzaTM site:<http://www.backcare.org.uk/>

0 returned results

A.34: Source: Fighting Back UK website

Interface / URL: <http://fightingbackuk.com/>
Database coverage dates: Information not found.
Search date: 19/06/17
Retrieved records: 0
Search strategy:

No search site function found on website.

Searched Google using: Senza site:<http://fightingbackuk.com/>
Searched Google using: SenzaTM site:<http://fightingbackuk.com/>

0 returned results

A.35: Source: Action on Pain website

Interface / URL: <http://www.action-on-pain.co.uk/>
Database coverage dates: Information not found.
Search date: 19/06/17
Retrieved records: 0
Search strategy:

Site wide search: Senza
Site wide search: SenzaTM

Searched Google using: Senza site:<http://www.action-on-pain.co.uk/>
Searched Google using: SenzaTM site:<http://www.action-on-pain.co.uk/>

0 returned results

A.36: Source: Pain Association Scotland website

Interface / URL: <http://www.painassociation.com/>
Database coverage dates: Information not found.
Search date: 19/06/17
Retrieved records: 0
Search strategy:

No search site function found on website.

Searched Google using: Senza site:<http://www.painassociation.com/>
Searched Google using: SenzaTM site:<http://www.painassociation.com/>

0 returned results

A.37: Source: Pain Concern website

Interface / URL: <http://painconcern.org.uk/>
Database coverage dates: Information not found.
Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<http://painconcern.org.uk/>

Searched Google using: SenzaTM site:<http://painconcern.org.uk/>

0 returned results

A.38: Source: Pain Relief Foundation website

Interface / URL: <http://www.painrelieffoundation.org.uk/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

No search site function found on website.

Searched Google using: Senza site:<http://www.painrelieffoundation.org.uk/>

Searched Google using: SenzaTM site:<http://www.painrelieffoundation.org.uk/>

0 returned results

A.39: Source: Pain UK website

Interface / URL: <https://painuk.org/>

Database coverage dates: Information not found.

Search date: 19/06/17

Retrieved records: 0

Search strategy:

Site wide search: Senza

Site wide search: SenzaTM

Searched Google using: Senza site:<https://painuk.org/>

Searched Google using: SenzaTM site:<https://painuk.org/>

A.40: Source: Nevro website – Clinical Evidence webpage

Interface / URL: <http://www.nevro.com/English/Physicians/Clinical-Evidence/default.aspx>

Database coverage dates: Information not found.

Search date: 26/06/17

Retrieved records: 0

Search strategy:

The studies cited on the Clinical Evidence webpage were screened. Duplicates of records already retrieved via other information sources were not retrieved.

4 references screened. All were duplicates of records already retrieved via other information sources. 0 were records retrieved.

A4: Evidence selection – PRISMA diagrams

Figure A1.1. PRISMA flow diagram showing studies assessed from the EAC’s replication of the company’s search strategy

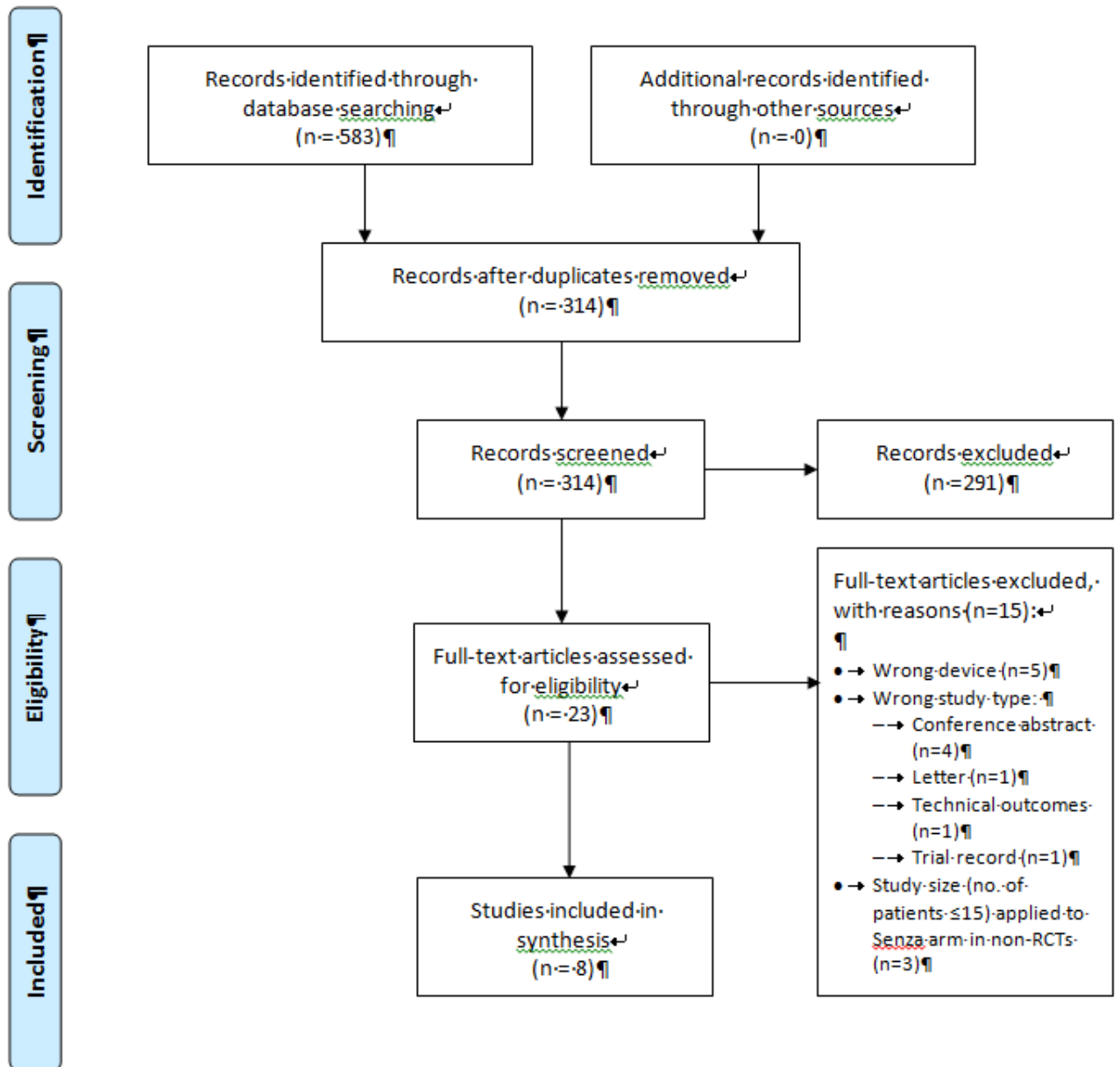
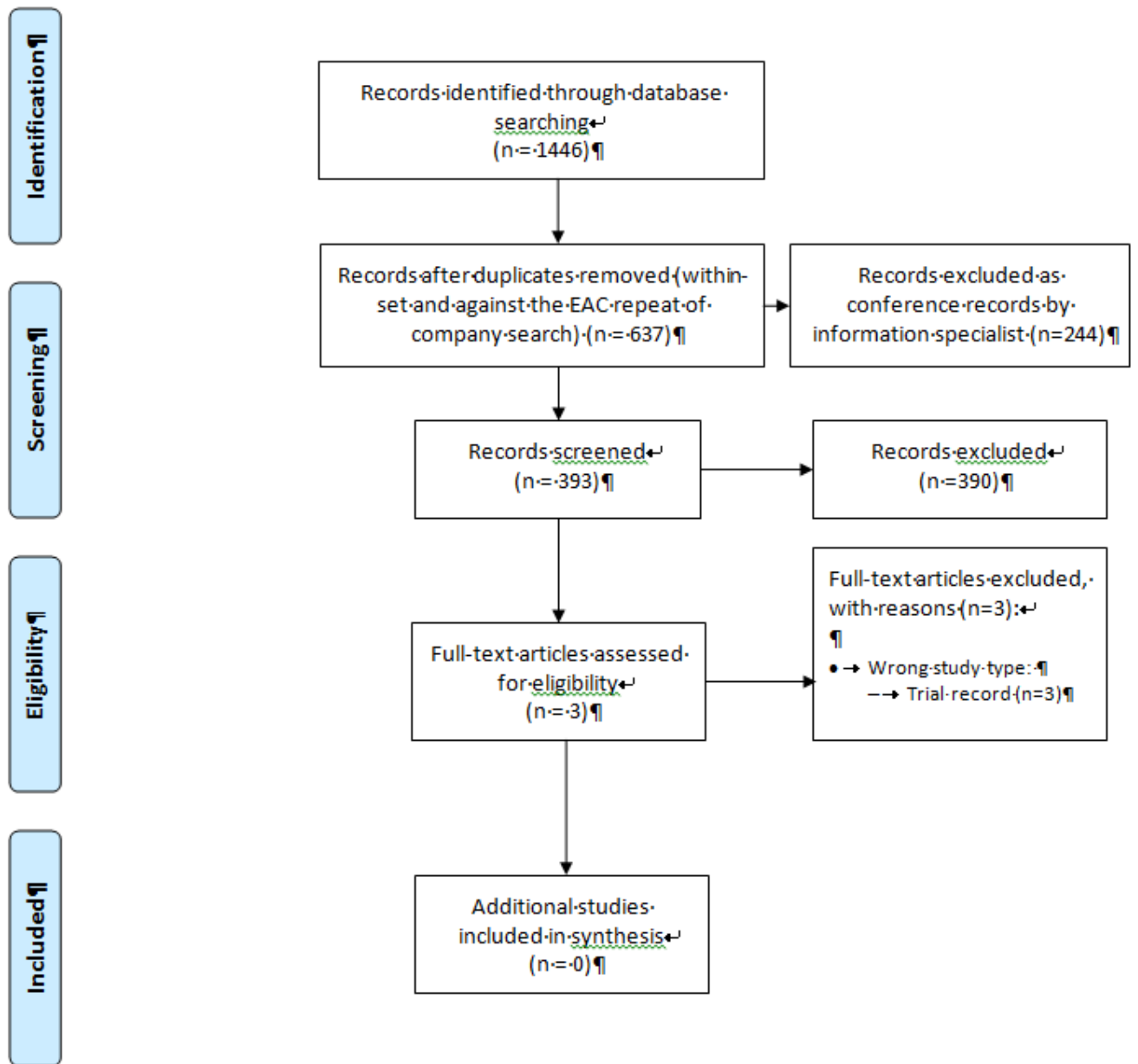


Figure A1.2. PRISMA flow diagram showing studies assessed from the additional EAC search strategy



A5: Critique of company's economic search strategy

Company's search strategies to identify economic evidence

The Peer Review of Electronic Search Strategies (PRESS) Checklist was used to inform the critique of the company's search strategies (McGowan *et al.*, 2010). The PRESS checklist is an evidence-based tool used to critically appraise literature search strategies. The PRESS project was funded by the Canadian Agency for Drugs and Technologies in Health (CADTH) and this approach to peer reviewing search strategies is supported by the Cochrane Collaboration's Information Retrieval Methods Group (Sampson *et al.*, 2008).

Search reporting

The company clearly states which bibliographic databases were used for the searches (Sections 8.1.1 and 10.3, Submission). The interface used for each database is reported, though there is a discrepancy between the interface reported for the MEDLINE search (PubMed) and some of the syntax reported for the PubMed strategy which is specific to Ovid and not appropriate for use in PubMed. The syntax *or/1-5* for example is not appropriate in PubMed. In addition, the PubMed strategy uses lower case Boolean *and*; in PubMed Boolean operators should be upper case. It is not possible to know however if the interface has been reported incorrectly, or if the strategy syntax has been reported incorrectly, or if there is an error in the actual running of the strategy. Search dates and result numbers for each bibliographic database are stated. The MTEP Submission Template indicates that the review of the economic evidence should be systematic and transparent. The search strategies for bibliographic databases are reported but are not described in sufficient detail to be fully transparent. The MTEP Submission Template states that the company should describe the strategies used to retrieve relevant health economics studies from the published literature *and* to identify all unpublished data. A search of internal documentation to identify unpublished studies is reported (Section 10.3.5, Submission) but no further details are given on the content of the internal documentation or the search methods used. It is therefore not possible to comment on the content of this documentation, or the appropriateness of the search methods used. No search date is provided for the search of internal documentation.

Search sources

The company searched all the resources indicated as a minimum requirement in the NICE submission template (MEDLINE, MEDLINE In-Process, Embase, NHS EED and EconLit). The resources searched by the company for published studies therefore represent a good selection of core bibliographic databases indexing healthcare economic evaluations. The selection could have been enhanced by the inclusion of other databases which include economic evidence, for example the HTA database.

The company conducted a search of internal documentation to identify unpublished studies. Although there would have been no added value to searching additional conference sources, given the submission eligibility criteria (which specifically excludes conference abstracts (Table 41, Submission)), the submission methodology could have been enhanced by searching additional sources for unpublished studies, for example the HTA database and trial registers (which can include economic evaluations).

Bibliographic databases: search strategy structure, search terms, syntax and restrictions

The search methods reported in the submission do not contain sufficient detail to be certain of the exact search strategies used, but enough information was provided for the EAC to make an informed judgement as to how the searches were conducted (for further details see Appendix A6) and the search strategies were critiqued on this basis.

The approach taken by the company to search strategy construction does not reflect conventional approaches to systematic literature review searches. In some databases (NHS EED and EconLit) rather than conducting one single search for each database, the reported methods indicate that for each database a number of short, separate searches were carried out, with results (where found) collected separately. In addition, rather than explicitly including distinct subject heading searches and free text searches across specific fields in databases such as PubMed and Embase, the company just searches across 'all fields'.

The search terms included in the bibliographic database strategies were limited in range given the systematic review context. No spelling errors were identified and the use of Boolean operators to combine terms was appropriate. As noted earlier there are potential issues with some of the reported syntax used for Boolean, though these may be due to reporting errors, rather than errors in the strategies as run. The limited range of variant terms potentially increased the risk of missing relevant studies. Search methodology would have been enhanced, for example, by including additional free-text terms to retrieve potential variants for the spinal cord stimulation concept (such as stimulation of the spinal cord, spinal cord electrostimulation/s, spinal cord stimulator/s). Similarly, search terms for the high frequency concept would have been enhanced by including potential free-text variants such as HF-10, 10khz and 10 kilohertz. The PubMed and Embase strategies combine the intervention terms with a limited set of terms related to economic evidence. It seems likely that these terms are intended to identify economic evaluations (the study design of interest as stated in the eligibility criteria). This being the case, search methodology would have been enhanced by using (or translating for PubMed and Elsevier Embase as appropriate) recognised sensitive search filters designed to identify economic evaluations in MEDLINE and Embase, for example those designed by the Centre for Reviews and Dissemination, University of York to identify economic evaluations in NHS EED¹². No truncation was used; methodology would have been

enhanced by the appropriate use of truncation, for example to search for variants of the device trade name such as Senza™. There was inconsistency in the choice of search terms used in different databases for the intervention concept, with no rationale given for this. The term SCS is included in the EconLit search for example as a variant for spinal cord stimulation, but not in any of the other search strategies. The EconLit strategy also includes terms related to neuromodulation / neurostimulation; again, these are not included in any of the other database strategies. Searches appear to be limited to results published from 2006, reflecting the submission eligibility criteria. The appropriateness of the company's eligibility criteria is discussed in [section 4.1.2](#). As the submission does not contain sufficient detail to be certain of the exact search strategies, it is not possible to tell if the date limits were applied correctly.

Currency of searches

The bibliographic database searches were conducted in January 2017, almost 6 months before the submission. A gap between search date and review completion is inevitable in any systematic review, but obviously relevant studies may have been published or added to the databases in this period. No search date is given for the search of internal documentation therefore it is not possible to ascertain currency for this search.

A6: Re-run of company's searches - economic evidence

As previously noted, the search methods reported in the submission do not contain sufficient detail to be certain of the exact search methods used, but enough information was provided for the EAC to make an informed judgement as to how the searches were conducted, and the searches were re-run on this basis. We assumed that search strategy reported for PubMed was actually run in PubMed using appropriate syntax for all lines (and that those lines in the reported strategy which were not appropriate to PubMed were due to a reporting error). We assumed that date limits had been applied correctly. We assumed that the redundant inclusion of the phrase *cost minimisation* twice in the PubMed, Ovid MEDLINE and Embase strategies was a reporting error, and that the company actually searched on either *cost minimisation* or *cost minimization*. In NHS EED it was assumed that line 1 was not a final result line (reflecting the numbers reported in the *Schematic for the systematic review of published health economic studies* (Figure 27, submission)).

The EAC searched EconLit and Embase via the Ovid interface; the company's Elsevier Embase and ProQuest EconLit strategies were translated for Ovid as appropriate.

It was noticeable that whilst the company retrieved 47 records in their database searches, when the EAC re-ran the searches only 18 records were retrieved. The

main difference was that the EAC retrieved 27 less records from the MEDLINE In-Process search. It is not possible to be certain why this was, though the fact that the company's final search line retrieved the same number of records (28) as one of the lines which was being combined using Boolean AND to produce the final line, indicates that there may potentially be some kind of error with the company's reporting of the strategy. We cannot be certain this is the case however; MEDLINE-In-Process is a dynamic database so it may be due to a difference in database content at the time of search.

Re-run company's searches – economic evidence: information resources

The information resources searched for the re-run company's searches are shown in Table A6.1.

Table A6.1: Re-run company's searches – economic evidence: databases and information resources searched

Database / information resource	Interface / URL
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Embase	OvidSP
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	OvidSP
EconLit	OvidSP
NHS Economic Evaluation Database (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/

Results of the searches were downloaded and imported into EndNote reference management software. The records were deduplicated using several algorithms.

Re-run company's searches – economic evidence: results

The search identified retrieved **18** records, with **16** records remaining for assessment after deduplication (Table A6.2).

Table A6.2: Re-run company's searches: results

Database / information resource	Records identified
PubMed	7
Embase	4
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	1
EconLit	6
NHS Economic Evaluation Database (NHS EED)	0
TOTAL	18

TOTAL after deduplication	16
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Re-run company's searches – economic evidence: full search strategies

A.1: Source: PubMed

Interface / URL: <https://www.ncbi.nlm.nih.gov/pubmed/>

Database coverage dates: 1946 to current. Updated daily.

Search date: 07/07/17

Retrieved records: 7

Search strategy:

The search was carried out using the advanced search interface. The search terms were searched across 'All Fields' (selected using the drop-down menu in the Builder).

- #19 Search (#8 AND #17) Filters: Publication date from 2006/01/01 to 2017/01/10
7
- #18 Search (#8 AND #17) 9
- #17 Search (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
204689
- #16 Search quality adjusted life years 15265
- #15 Search incremental cost-effectiveness ratio 4571
- #14 Search economic model 46569
- #13 Search cost-effective 70977
- #12 Search cost utility 13234
- #11 Search cost benefit 91941
- #10 Search economic evaluation 90905
- #9 Search ((cost minimisation) OR cost minimization) 2138
- #8 Search (#6 AND #7) 761
- #7 Search spinal cord stimulation 21977
- #6 Search (#1 OR #2 OR #3 OR #4 OR #5) 561956
- #5 Search hf10 63
- #4 Search senza 20
- #3 Search nevro 45
- #2 Search 10 khz 7441
- #1 Search high frequency 556175

**A.2: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
July 06, 2017**

Interface / URL: OvidSP

Database coverage dates: Updated Daily

Search date: 07/07/17

Retrieved records: 1

Search strategy:

- 1 high frequency.af. (8260)
- 2 10 khz.af. (490)
- 3 nevro.af. (8)

- 4 senza.af. (100)
- 5 hf10.af. (8)
- 6 or/1-5 (8816)
- 7 spinal cord stimulation.af. (379)
- 8 6 and 7 (21)
- 9 (cost minimisation or cost minimization).af. (145)
- 10 economic evaluation.af. (1143)
- 11 cost benefit.af. (978)
- 12 cost utility.af. (582)
- 13 cost-effective.af. (10532)
- 14 economic model.af. (220)
- 15 incremental cost-effectiveness ratio.af. (558)
- 16 quality adjusted life years.af. (779)
- 17 or/9-16 (12900)
- 18 8 and 17 (1)
- 19 limit 18 to yr="2006 -Current" (1)

A.3: Source: Embase

Interface / URL: OvidSP

Database coverage dates: 1974 to 2017 July 06

Search date: 07/07/17

Retrieved records: 4

Search strategy:

- 1 high frequency.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (49241)
- 2 10 khz.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (862)
- 3 nevro.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (84)
- 4 senza.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (187)
- 5 hf10.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (145)
- 6 or/1-5 (50138)
- 7 spinal cord stimulation.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (4221)
- 8 6 and 7 (294)
- 9 cost minimization.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (2230)
- 10 cost minimisation.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (263)
- 11 economic evaluation.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (13666)
- 12 cost benefit.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (38881)

- 13 cost utility.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (7217)
- 14 cost-effective.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (68387)
- 15 economic model.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (2075)
- 16 incremental cost-effectiveness ratio.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (5759)
- 17 quality adjusted life years.af. and ("2006" or "2007" or "2008" or "2009" or "2010" or "2011" or "2012" or "2013" or "2014" or "2015" or "2016" or "2017").yr. (7876)
- 18 or/9-17 (119009)
- 19 8 and 18 (4)

A.4: Source: Econlit

Interface / URL: OvidSP

Database coverage dates: 1886 to June 2017

Search date: 07/07/17

Retrieved records: 6

Search strategy:

- 1 (high frequency and spinal cord stimulation).af. (0)
- 2 (high frequency and SCS).af. (0)
- 3 spinal cord stimulation.af. (0)
- 4 10 khz.af. (0)
- 5 nevo.af. (0)
- 6 senza.af. (36)
- 7 or/1-6 (36)
- 8 limit 7 to yr="2006 -2017" (21)
- 9 limit 8 to english (3)
- 10 hf10 therapy.af. (0)
- 11 neuromodulation.af. (3)
- 12 neurostimulation.af. (0)
- 13 or/10-12 (3)
- 14 limit 13 to yr="2006 - 2017" (3)
- 15 9 or 14 (6)

A.5: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: <https://www.crd.york.ac.uk/CRDWeb/>

Database coverage dates:

Search date: 07/07/17

Retrieved records: 0

Search strategy:

Search terms were limited to 'any field' using the drop down option

1	(spinal cord stimulation) IN NHSEED FROM 2006 TO 2017	9
2	(spinal cord stimulation AND high frequency) IN NHSEED FROM 2006 TO 2017	0
3	(spinal cord stimulation AND 10 khz) IN NHSEED FROM 2006 TO 2017	0
4	(spinal cord stimulation AND nevro) IN NHSEED FROM 2006 TO 2017	0
5	(spinal cord stimulation AND senza) IN NHSEED FROM 2006 TO 2017	0
6	(spinal cord stimulation AND hf10) IN NHSEED FROM 2006 TO 2017	0

0 results were retrieved

Appendix B: Critical appraisal of included studies.

Table B1. *Critical appraisal of the PROCESS trial (Kumar et al., 2007).*

	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	Random computer-generated blocks (random sequence of either 2 or 4 patients) on a per site basis. CMM group had significantly higher back pain scores at baseline.	Unclear risk of selection bias
	Allocation concealment	"The randomisation was electronically locked and could only be accessed after a patient entered the trial". Allocation administered from central location.	Low risk of selection bias
Performance bias	Blinding of participants and personnel*	Open label trial, no blinding was possible. Main outcomes were subjective.	High risk of performance bias
Detection bias	Blinding of outcome assessment*	Blinding of investigators was not attempted.	High risk of detection bias
Attrition bias	Incomplete outcome data*	ITT analysis of primary outcome. Patient flow documented. However, high attrition rate and extensive cross over occurred.	High risk of attrition bias
Reporting bias	Selective reporting	Primary outcome pre-specified (ISRCTN77527324) and power calculation performed.	Low risk of bias
Other bias	Anything else, ideally pre-specified.	Trial funded by Medtronic who had access to Trial Steering Committee.	Unclear risk of bias

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

Table B2. *Critical appraisal of surgical RCT (North et al., 2005)*

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	Consecutive opening of "computer-generated random assignments" in opaque envelopes. Only 60/100 eligible patients randomised.	High risk of selection bias
	Allocation concealment	Randomisation administered by an "outside biostatistician". No comparison of groups at baseline.	High risk of selection bias
Performance bias	Blinding of participants and personnel*	Open label trial. Impossible to blind patients or treating physicians to allocation. Subjective outcomes.	High risk of performance bias
Detection bias	Blinding of outcome assessment*	Investigators were not blinded.	High risk of performance bias
Attrition bias	Incomplete outcome data*	Very large drop out prior to and after randomisation. Very large crossover to alternative arm of trial (in fact this was one of the principal outcomes).	High risk of attrition bias
Reporting bias	Selective reporting	Primary outcome not clearly defined and no protocol reported. Power calculation reported but not clearly described. Unclear how ITT was implemented or how to interpret results with such a large cross over and loss to follow up.	High risk of reporting bias
Other bias	Anything else, ideally pre-specified.	Study funded by Medtronic and potential conflict of interest from providers of technology.	High risk of bias

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

Table B3. *Critical appraisal of SENZA-RCT (Kapural et al., 2015).*

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	Permuted block randomisation. Stratification by gender and primary source of pain (back or leg). Some differences in baseline characteristics observed.	Unclear risk of selection bias.
	Allocation concealment	Randomisation was administered centrally. However, it is unclear how information on allocation was relayed to providers.	Unclear risk of selection bias.
Performance bias	Blinding of participants and personnel*	This was an open label trial. No blinding was attempted. Blinding of participants and personnel was not possible due to differences in the implant procedure, technical differences between devices, and sensation of paraesthesia. Nearly all outcomes were subjective and susceptible to suggestion.	High risk of performance bias.
Detection bias	Blinding of outcome assessment	This was an open label trial. Assessors, investigators, and statisticians were not blinded. Outcomes were patient orientated and largely subjective.	High risk of detection bias.
Attrition bias	Incomplete outcome data	A comprehensive subject flow diagram was reported in the study. This included reasons for loss to follow up at 12 and 24 months. ITT analysis was used for the primary outcome. The following attrition rate was observed for Senza (n=101) and traditional SCS (n=97) respectively*: Trial stage: 96%, 95%. Permanent implant received: 89%, 84% 12 month follow up:	High risk of attrition bias.

		88%, 82% 24 month follow up: 84%, 73%. Loss to follow up was not equivalent between arms and was a serious to intermediate threat to validity at 24 months**. Cross over to alternative intervention was not reported.	
Reporting bias	Selective reporting	Trial protocol reported at NCT01609972 but not updated for ≥ 2 years. Trial was designed as an inferiority RCT but superiority outcomes extensively reported. Primary outcome defined in protocol and power calculation performed: however rationale for margin of inferiority not reported and sample number substantially less than reported in protocol (n=356). Many results not reported using ITT analysis. Explantation rates not published. Some secondary outcomes may be reported on a <i>post hoc</i> basis. However, adjustment for multiple comparisons (Bonferroni) performed.	Unclear risk of reporting bias.
Other bias	Anything else, ideally pre-specified.	Funding for study provided by Nevro corp. Company's non-financial role in study conduct not reported.	Unclear risk of bias.
*From 24 month follow up paper (Kapural <i>et al.</i> , 2016c).			
** Acceptable loss to follow up (Fewtrell <i>et al.</i> , 2008)			

Table B4. *Critical appraisal of SENZA-EU study.*

SENZA-EU (Van Buyten <i>et al.</i> , 2013; Al-Kaisy <i>et al.</i> , 2014)	
Is the study based on a representative sample selected from a relevant population?	Yes Patients prospectively enrolled from two centres (UK and Belgium). However, patient selection method not described.
Are criteria for inclusion explicit?	Yes “primary diagnosis of chronic back pain (defined as lumbosacral pain) with or without leg pain with intensity of at least 5.0 out of 10.0 (average score over the last 30 days) on the VAS; have failed to respond to at least six months of conventional treatment including pharmacologic treatment, physical therapy, epidural injections, and/or radiofrequency therapy”.
Did all individuals enter the study at a similar point in their disease progression?	Yes Patients had long-term back pain, although distribution was wide: Mean duration (years): 9.7 ± 8.1 (SD) Back pain (VAS): 8.4 ± 1.2 Leg pain (VAS): 5.4± 3.2
Was follow up long enough for important events to occur?	Yes Follow up 24 months
Were outcomes assessed using objective criteria or was blinding used?	No Primar outcome of pain measurement by VAS is subjective, as are secondary outcomes of ODI and sleep disturbance. No blinding performed.
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	Yes Limited comparison of baseline characteristics between patients receiving permanent implantation and non-responder to trial
Abbreviations. ODI: Oswestry Disability Index; SD: Statistical Deviation; VAS: Visual analogue scale.	

Table B5. *Critical appraisal of Russo et al. (2016).*

Case series (Russo et al., 2016)	
Is the study based on a representative sample selected from a relevant population?	Unclear Retrospective analysis of data from 3 Australian pain centres. The patients studied “were not candidates for, or responders to, traditional SCS therapy”.
Are criteria for inclusion explicit?	No No formal inclusion or exclusion criteria. Patients had a range of chronic intractable pain distributions, including back only, leg only, back and leg, head and neck pain, neck and shoulder/arm pain, and other complex pain patterns. However, 16.8% of patients had different location recorded or data were absent.
Did all individuals enter the study at a similar point in their disease progression?	No Case mix was heterogeneous in terms of pain aetiology and previous treatments.
Was follow up long enough for important events to occur?	Unclear Follow up was recorded at 6 months but there was substantial patient attrition.
Were outcomes assessed using objective criteria or was blinding used?	No Subjective outcomes including NPRS assessment of pain, ODI, and sitting tolerance. No blinding performed.
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	No Subgroup comparison not performed.
Abbreviations. NPRS: Numerical pain rating scale; ODI: Oswestry Disability Index.	

Table B6. *Critical appraisal of Tiede et al. (2013).*

“Before and after” study (non-randomised) (Tiede <i>et al.</i> , 2013)	
Is the study based on a representative sample selected from a relevant population?	Unclear Multicentre using prospective enrolment, mainly patients with FBSS. Method of enrolment not described.
Are criteria for inclusion explicit?	Yes Inclusion criteria “source of chronic pain predominantly from the back with an intensity of at least 5.0 cm on a Visual Analog Scale (VAS, 0 [no pain] to 10 [worst pain imaginable]).... already confirmed as a candidate for conventional SCS therapy”.
Did all individuals enter the study at a similar point in their disease progression?	Unclear Duration of back pain not recorded. Most (91.7%) of patients reported as having more than one previous attempt at back surgery.
Was follow up long enough for important events to occur?	No Short-term study (7 to 11 days) with inadequate wash out phase. SCS generally recognised to have long-term benefits.
Were outcomes assessed using objective criteria or was blinding used?	No Outcomes were subjective and included pain as measured by VAS and patient preference. Study was open label without randomisation of sequence order.
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	No Comparison was “before and after” but no randomisation of order and no subgroup analysis.
Abbreviations. VAS: Visual analogue scale.	

Table B7. *Critical appraisal of Rapcan et al. (2015).*

Case series (Rapcan et al., 2015)	
Is the study based on a representative sample selected from a relevant population?	Unclear Patients prospectively enrolled from four Slovakian pain centres. Enrolment method not reported.
Are criteria for inclusion explicit?	Yes Inclusion criteria :”primary diagnosis of chronic back pain with or without leg pain, intensity of at least 6 out of ten on Visual Analog Scale (VAS), failure of conventional treatment including pharmacological treatment, physical therapy, epidural injections”.
Did all individuals enter the study at a similar point in their disease progression?	Yes Patients had long-term back and leg pain. Average pain duration stated as 7.8 ± 5 years (SD).
Was follow up long enough for important events to occur?	Yes Follow up of 12 months
Were outcomes assessed using objective criteria or was blinding used?	No Primary outcome was reduction in pain using VAS, performance status, and patient satisfaction (subjective). Blinding not performed.
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	No Description of “special subgroup” who required alternating treatment with Senza and conventional SCS for effective pain relief.
Abbreviations. SD: Statistical Deviation; VAS: Visual analogue scale.	

Table B8. *Critical appraisal of Al-Kaisy et al. (2017).*

Case series, “proof of concept” study (Al-Kaisy et al., 2017)	
Is the study based on a representative sample selected from a relevant population?	Unclear Prospective study in single centre (Guy’s hospital). Method of patient recruitment unclear. Patients had predominant back pain and were surgically naïve (i.e. not FBSS)
Are criteria for inclusion explicit?	Yes Inclusion criteria include “symptoms of axial low back pain for at least 6 months, with a minimum intensity of 5/10 on a Visual Analogue Scale (VAS); predominant low back pain (VAS back scores being 2 cm greater than leg pain if present); failure to respond to conventional medical management”. Detailed exclusion criteria (reasons) tabulated at patient level.
Did all individuals enter the study at a similar point in their disease progression?	Yes Patients had long-term chronic pain of 7.06 ± 5.8 (SD) years.
Was follow up long enough for important events to occur?	Yes Follow up of 12 months
Were outcomes assessed using objective criteria or was blinding used?	No Main outcomes were pain reduction (VAS) functional improvement (ODI), patient satisfaction, sleep quality, and HrQoL status (subjective outcomes) No blinding was performed.
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	No Subgroup comparisons not performed.
Abbreviations. ODI: Oswestry Disability Index; SD: Statistical Deviation; VAS: Visual analogue scale.	

Appendix C: Planned and on-going studies

Table C. List of identified study protocols and on-going studies.

Trial Identification and country of origin	Study design	Population	Date and sponsor	Source of identification
Belgium/Senza [™] Registry (unidentified)	Registry	Unknown characteristics 120 participants	Expected completion: January 2018. Sponsor unknown.	Identified by company. Not identified by EAC, details unknown.
(ACTRN12614000665639, 2014b) Australia	Non-comparative single-armed observational study. Active treatment: Senza HF10.	Patients with chronic back pain with or without leg pain following spinal surgery. 100 participants.	First enrolment 5.11.2013 Nevro Corp.	Identified by company. Identified by EAC using additional literature search.
(ACTRN12614000236695, 2014a) Australia	Randomised double blind sham controlled cross over RCT Active treatment: Senza HF10. Comparator: sham (placebo)	Patients with persistent back pain with or without leg pain (for 6 months). 17 participants.	Not yet recruiting. Self funded (no sponsor)	Identified by EAC by using additional literature search.
(NTR4965, 2014) Netherlands study	Single armed case series (12 months). Active treatment: Senza HF10.	Patients with FBSS. 55 participants.	Last record December 2015. Nevro Corp.	Identified by EAC by using additional literature search.

Trial Identification and country of origin	Study design	Population	Date and sponsor	Source of identification
(NCT02689375, 2015) Leeds study	Prospective case series. Active treatment: Senza HF10	Patients with chronic predominant low back pain of neuropathic origin, for a minimum of 6 months. 25 participants.	Last record February 2016. No sponsor identified.	Identified by company and by EAC repeat of company's literature search.
(ISRCTN547086 53, 2016) Australia	Single centre prospective non randomised study. Active treatment: Senza HF10. Comparator: varying programme settings.	Patients with Failed Back Surgery Syndrome (FBSS), already successfully using Senza Therapy. Target: 20 participants.	Study protocol completed April 2017, not yet found in published literature. Nevro Corp.	Identified by EAC repeat of company's literature search. Omitted by company from their submission.
(ISRCTN136747 19, 2017) SENZA-Medial & Lateral Australia	Single centre prospective single-blind non randomised feasibility study. Active treatment: Senza HF10. Comparator: varying lead placement during trial phase of implant.	Patients with chronic, intractable predominant low back pain. Target: 20 participants.	Start date 19/04/2016. Overall trial end date 09/06/2018. Nevro Corp.	Identified by EAC repeat of company's literature search. Omitted by company from their submission.

Trial Identification and country of origin	Study design	Population	Date and sponsor	Source of identification
(ISRCTN11720855, 2017) Australia	Single armed multi-centre prospective observational clinical study. Active treatment: Senza HF10.	Patients with chronic, intractable predominant leg pain with a permanent implant. 90 participants.	Start date 07/10/2016. Overall trial end date 07/10/2019. Nevro Corp.	Identified by EAC repeat of company's literature search. Omitted by company from their submission.
(ISRCTN13607429, 2016) Belgium	Multi-centre prospective interventional randomised clinical study. Active treatment: Senza HF10. Comparator: varying programme settings.	Patients with predominant back pain after failed back surgery. Target: 20 participants.	Start date 07/03/2016. Overall trial end date 13/12/2018. Nevro Corp.	Identified by EAC repeat of company's literature search. Omitted by company from their submission.
(NCT02385201, 2015) SENZA-ULN USA	Single armed multi-centre prospective clinical trial. Active treatment: Senza HF10.	Patients with chronic, intractable pain of the upper limbs and/or neck. 75 participants.	Start date June 2015. Estimated study completion date September 2017. Nevro Corp.	Identified by EAC repeat of company's literature search. Omitted by company from their submission.
(NCT02703818, 2016) UEP USA	Single armed multi-centre prospective clinical trial. Active treatment: Senza HF10.	Patients with chronic, intractable pain of the upper extremities. 70 participants.	Start date February 2016. Estimated study completion date March 2018. Nevro Corp.	Identified by EAC repeat of company's literature search. Omitted by company from their submission.

Trial Identification and country of origin	Study design	Population	Date and sponsor	Source of identification
PROVA study[57] ⁵⁷ CA2011 PROVA BE Belgium (van Buyten <i>et al.</i> , 2011)	Prospective double blind cross over study. Active treatment: Senza HF10. Comparator: sham (placebo).	Patients with FBSS and VAS \geq 5 cm. Pain radiating from L3, L4, L5, S1.	Recruitment end date: 13 th December 2017. Nevro Corp.	Identified by company and by EAC during repeat of company's literature search.
Abbreviations. FBSS: failed back surgery syndrome; VAS: visual analogue scale.				

Appendix D: Validation of *de novo* model

Table D1. Description of Excel spreadsheet used in model.

	Sheet name	Description
Key executable inputs and results	Title	Title sheet. "Cost-consequence analysis of HF10™ therapy vs. Traditional low-frequency SCS"
	ShortTermEfficacy	Input parameters for the decision tree aspect of model (6 months in base case). Schematic description of decision tree.
	LongTermEfficacy	Input parameters for the Markov model (15 years). Schematic description of Markov model.
	StateRewards	Cost values associated with clinical states in the model. Utility values also included for completeness.
	Results_Discounted	Top level results of the analysis (costs and incremental costs).
	Results_DiscountedGranular	Breakdown of cost results by clinical state.
Simulation and longitudinal results	CostResultsOverTime	Longitudinal cost results, including graphical representation of cumulative costs over time.
	ReportTables	Breakdown of parameters with distributions (confidence intervals).
	ModelParameters	Reports all model parameters (probabilities, costs, utilities) and distributional information to allow for probabilistic analysis. Beta distributions used for probabilities and utilities. Gamma distributions used for costs.
	Tornado Diagram Data	Reports data informing the tornado diagram (univariate analysis).
	Tornado Diagram.	Tornado graph.
	Simulations	Data generated from probabilistic analysis (n = 5000). Runs from embedded Macro (MTechAccess_Simulation).
	Multiple_CEAC	Data for cost effectiveness acceptability curve, and plot of curve.
	MarkovTrace	Graphs plotting proportions of patients in each clinical state over time.
	PtFlow_HF10	Data and graph plotting proportion of patients who were initiated on HF10 treatment receiving each intervention over time.
	PtFlow_TR	Data and graph plotting proportion of patients who were initiated on low frequency SCS treatment receiving each intervention over time.
DT-Engine_HF10	Calculation of decision tree for patients	

	Sheet name	Description
		receiving HF10 therapy.
	Markov_Engine_HF10	Calculation of clinical states in Markov model for patients starting long-term management on HF10 therapy.
	DT_Engine_TNR	Calculation of decision tree for patients receiving low frequency SCS.
	Markov_Engine_TR	Calculation of clinical states in Markov model for patients starting long-term management on low frequency SCS.
Additional inputs	Inflation_Calc	Adjustment of costs in literature through HCHS index.
	Notation	Description of parameters for national life tables.
	2013-2015	Life expectancy data from ONS.
	ShortTermEfficacyLive	Live efficacy data for decision tree.
	LongTermEfficacyLive	Live efficacy data for Markov model.
	StateRewardsLive	Live cost and utility data for Markov model.

Table D2. Assumptions used in the economic model.

Assumption used in model	Justification made by company	EAC comment
Complications occur equally in patients with optimal and sub-optimal pain relief.	Same assumption used in NICE TA 159 model. No other publicly available data.	Complication rate data from systematic review of mainly observational studies of people with FBSS undergoing low frequency SCS (Taylor <i>et al.</i> , 2005). Several assumptions regarding population, management and temporal factors. Substantial uncertainty.
Proportion of patients receiving a back reoperation: 5%	Same assumption used in NICE TA 159 model. No other publicly available data.	Estimate of reoperation rate derived from surgical RCT (North <i>et al.</i> , 2005). Not transparent how this value was derived. Substantial uncertainty.
Device longevity of TNR-SCS: 4 years	Assumption based the figure used in NICE TA 159 model and Taylor <i>et al.</i> (2010). 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.	Source of assumption was observational study by Kumar <i>et al.</i> (2006b). Range of 2 to 10 years used in TA 159 model. Substantial uncertainty.
Device longevity of TR-SCS: 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.	Estimate of battery life appear reasonable. There is some uncertainty but general consensus from clinical experts is 10 years is a conservative estimate.
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 TA 159 model. No other publicly available data.	Estimate derived from PROCESS study (Kumar <i>et al.</i> , 2007). Requires extrapolation as patients did not not have prior failed SCS treatment. Substantial uncertainty.

Assumption used in model	Justification made by company	EAC comment
All CMM costs are comparable with that of Kumar <i>et al.</i> (2007) (PROCESS study) (5) and applied equally in patients with optimal and sub-optimal pain relief	Same assumption used in NICE TA 159 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.	Assumes CMM has remained relatively unchanged since TA 159 (2008), for example use of drugs, availability of generics, new generation drugs. EAC agrees the assumption is likely to be conservative.
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.	The EAC agrees this is likely to be a conservative assumption (see Section 4.2.8).
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 TA 159 accepted the clinical outcomes of TNR-SCS and TR-SCS would be equivalent.	The EAC has confirmed with clinical experts that other than device longevity, there are no important differences between the rechargeable and non-rechargeable technologies. TA 159 assumed equivalence other than for longevity (Simpson <i>et al.</i> , 2008)
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).	In the model a patient can go from optimal to suboptimal pain relief with SCS, but not the other way. The EAC accepts there is no data to support the latter transition. However, the company's reference to 4 year retrospective data is from an unpublished conference abstract. It is unreasonable to extrapolate the prospective data from available clinical trials beyond their longest follow up dates.

Assumption used in model	Justification made by company	EAC comment
		Considerable uncertainty surrounding this assumption but it is from original model (TA 159).
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 TA 159 model.	The EAC accepts this assumption that there is no incremental difference in mortality risks between SCS types.
Abbreviations. CMM: conventional medical management; FBSS: failed back surgery syndrome; SCS: spinal cord stimulation; TNR-SCS: traditional low-frequency non-rechargeable spinal cord stimulation; TR-SCS: traditional low-frequency rechargeable spinal cord stimulation.		

Table D3. *Costs parameters used in de novo economic model.*

Cost parameter		Base case value (95% CI)	EAC comment*
SCS trial (suitability for permanent implantation)		£5,281 (£3,441 to £7,931)	Source: TA 159 (Taylor <i>et al.</i> , 2010) Primary source from retrospective Canadian analysis with bottom up costing (Kumar <i>et al.</i> , 2006b) with unit prices substituted with UK equivalents. Costs include cost for consultation, investigations, surgery, electrode and hospital charges.
Failed SCS trial (electrode removal)		£2,140 (£921 to £3,593)	Source: TA 159 (Taylor <i>et al.</i> , 2010) "It is assumed that the cost of failed trial stimulation is the same as the cost for device explant" (Simpson <i>et al.</i> , 2008) (See below).
Permanent SCS implantation	HF10	£16,648 (£13,116 to £21,421)	Source: published economic model (Annemans <i>et al.</i> , 2014). This study stated "The acquisition cost for the HF10 SCS system was supplied by the manufacturer."
	TNR-SCS	£11,281 (£8,888 to £14,516)	Source: (Taylor <i>et al.</i> , 2010), adjusted for inflation. Cost of device only (procedural costs omitted).
	TR-SCS	£17,422 (£13,726 to £22,418)	Source: (Taylor <i>et al.</i> , 2010), adjusted for inflation. Primary source as above but with higher device acquisition cost.
SCS explantation		£2,140 (£0 to £3,015)	Source: TA 159 (Taylor <i>et al.</i> , 2010). Primary source from retrospective Canadian analysis with bottom up costing (Kumar <i>et al.</i> , 2006b) with unit prices substituted with UK equivalents. Includes two GP consultations, a neurosurgical consultation, a surgeon's fee, and hospital charges.
SCS related complication		£740 (£241 to £1,869)	Source: TA 159 (Taylor <i>et al.</i> , 2010). Primary source from retrospective Canadian analysis with bottom up costing (Kumar <i>et al.</i> , 2006b) with unit prices substituted with UK equivalents. Includes electrode, displaced electrode, hardware malfunction, biological, and infection costs.
Drug pain therapy: CMM alone (6 months)		£3,167 (£0 to £8,412)	Source: TA 159 (Taylor <i>et al.</i> , 2010). Primary calculation of unit use from PROCESS trial (Kumar <i>et al.</i> , 2007). Unit prices substituted for UK equivalents using BNF and other data.
Non-drug pain therapy: CMM alone (6 months)		£956 (£0 to £1,157)	Source: TA 159 (Taylor <i>et al.</i> , 2010). Primary calculation of resource use taken from PROCESS trial (Kumar <i>et al.</i> , 2007). Includes cost of physical rehabilitation, psychological rehabilitation, acupuncture, massage and TENS.
Drug pain therapy : SCS + CMM (6 months)		£2,012 (£0 to 8,412)	Source: TA 159 (Taylor <i>et al.</i> , 2010). Primary calculation of unit use from PROCESS trial (Kumar <i>et al.</i> , 2007). Cost reduction relative to CMM alone

Cost parameter	Base case value (95% CI)	EAC comment*
Non-drug pain therapy: SCS + CMM	£33 (£0 to £40)	reflects reduced drug use. Source: TA 159 (Taylor <i>et al.</i> , 2010). Primary calculation of resource use taken from PROCESS trial (Kumar <i>et al.</i> , 2007). Cost reduction relative to CMM alone reflects reduced non-drug use.
<p>Abbreviations. BNF: British National Formulary (BNF); CMM: conventional medical management (alone); HF10: TNR-SCS, traditional low-frequency nonrechargeable spinal cord stimulation; TR-SCS, traditional low-frequency rechargeable spinal cord stimulation; Senza HF10 therapy; SCS: low spinal cord stimulation; TENS: transcutaneous electrical nerve stimulation.</p> <p>* All prices inflated to 2016 levels (Curtis and Burns, 2016)</p>		

Table D4. EAC validation of clinical parameters used to inform initial Markov proportions and transitional probabilities.

	Model parameter	Intervention*	Base case value (95% CI)	Company's source	EAC comment
Decision tree	Trial success (leading to permanent implant)	HF 10	92.8% (87.6% to 97.9%)	SENZA-RCT (Kapural <i>et al.</i> , 2015)	The EAC has confirmed these values from the literature (CI not reported but calculated assuming binomial distribution).
		LF SC S	88.0% (81.4% to 94.7%)		
	Optimal pain relief at 6 months	HF 10	80.9% (72.7% to 89.1%)	SENZA-RCT (Kapural <i>et al.</i> , 2015)	
		LF SC S	54.4% (43.5% to 65.2%)		
		CM M	9.3% (8.4% to 10.2%)	TA 159 model (Taylor <i>et al.</i> , 2010)	

	Model parameter	Intervention*	Base case value (95% CI)	Company's source	EAC comment
Markov state transition model					
	Explantation rate (Year 3 onwards)	HF 10 LF SCS	3.2% (0% to 15.8%)	TA 159 (Simpson <i>et al.</i> , 2008)	Data from long-term observational study (Kumar <i>et al.</i> , 2006a). Equivalence between SCS technologies is probably a conservative assumption (as LF SCS can cause paraesthesia).
	Annual death rate	All	0.8% (0.7% to 0.9%)	Office of National Statistics	Mean unadjusted adult death rate. As there is no differential in death rate between intervention cohorts, death rate does not affect results.
Proportion of patients receiving a reoperation per annum	CM	5.0% (4.5% to 5.5%)	TA 159 (Simpson <i>et al.</i> , 2008)	Primary data from surgical RCT (North <i>et al.</i> , 2005). Considerable uncertainty in this estimate.	
Proportion of	CM	19.0%	TA 159	Primary data from RCT trial using "as treated" analysis (North <i>et al.</i> , 2005). Based on small sample size (3/16	

Model parameter	Intervention*	Base case value (95% CI)	Company's source	EAC comment
patients achieving optimal pain relief post surgery after a reoperation		(17.1% to 20.9%)	(Simpson <i>et al.</i> , 2008)	patients) so potential for first order uncertainty.
<p>Abbreviations. CMM: conventional medical management (alone); HF10: Senza HF10 therapy; LF SCS: low frequency spinal cord stimulation</p> <p>* LF SCS devices assumed to be equivalent. Note CMM is not a comparator but part of the Markov pathway for both HF10 and LF SCS.</p>				