Review report of MTG41: Senza spinal cord stimulation system for delivering HF10 therapy to treat chronic neuropathic pain

This medical technology guidance was published in January 2019.

All medical technology guidance is usually reviewed 3 years after publication, unless NICE become aware of significant new information before the expected review date.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance will be updated, amended, remain unchanged (static list) or withdrawn.

Produced by: Newcastle External Assessment Group (EAG)

Authors: Rachel O'Leary, Clinical Scientist, NuTH
Kim Keltie, Lead Healthcare Scientist, NuTH
Matthew Reiling, Research Scientist, NuTH
Humayra Dervin, Clinical Scientist, NuTH
Emma Belilios, Project Coordinator, NuTH
Michael Drinnan, Head of Service – Clinical Engineering, NuTH

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Karen Sanderson, Nurse Consultant, Guy's and St Thomas' NHS Foundation Trust

Girish Vajramani, Consultant Neurosurgeon, University Hospital Southampton NHS Foundation Trust

Sarah Love-Jones, Consultant in Pain Medicine and Anaesthesia, North Bristol NHS Trust

Heather Williams, Nurse Consultant (Chronic Pain), the Newcastle upon Tyne Hospitals NHS Foundation Trust

1. Original objective of guidance

To assess the clinical and cost effectiveness of Senza spinal cord stimulation system for delivering HF10 therapy to treat chronic neuropathic pain.

2. Current guidance recommendations

1.1 The case for adopting Senza spinal cord stimulation (SCS) for delivering HF10 therapy as a treatment option for chronic neuropathic back or leg pain after failed back surgery is supported by the evidence. HF10 therapy using Senza SCS is at least as effective as low-frequency SCS in reducing pain and functional disability, and avoids the experience of tingling sensations (paraesthesia).

1.2 Senza SCS for delivering HF10 therapy should be considered for patients:

- with residual chronic neuropathic back or leg pain (at least 50 mm on a 0 mm to 100 mm visual analogue scale) at least 6 months after back surgery despite conventional medical management and
- who have had a successful trial of stimulation as part of a wider assessment by a multidisciplinary team.

1.3 Patients with other causes of neuropathic pain were included in the evaluation and may be considered for HF10 therapy using Senza SCS but any additional benefits compared with low-frequency SCS are less certain. Cost modelling indicates that, over 15 years, HF10 therapy using Senza SCS has similar costs to low-frequency SCS using either a rechargeable or non-rechargeable device.

1.4 Clinicians implanting SCS devices including Senza should submit timely and complete data to the UK Neuromodulation Registry.

1.5 When assessing the severity of pain and the trial of stimulation, the multidisciplinary team should be aware of the need to ensure equality of access to treatment with SCS. Tests to assess pain and response to

SCS should take into account a person's disabilities (such as physical or sensory disabilities), or linguistic or other communication difficulties, and may need to be adapted.

3. Methods of review

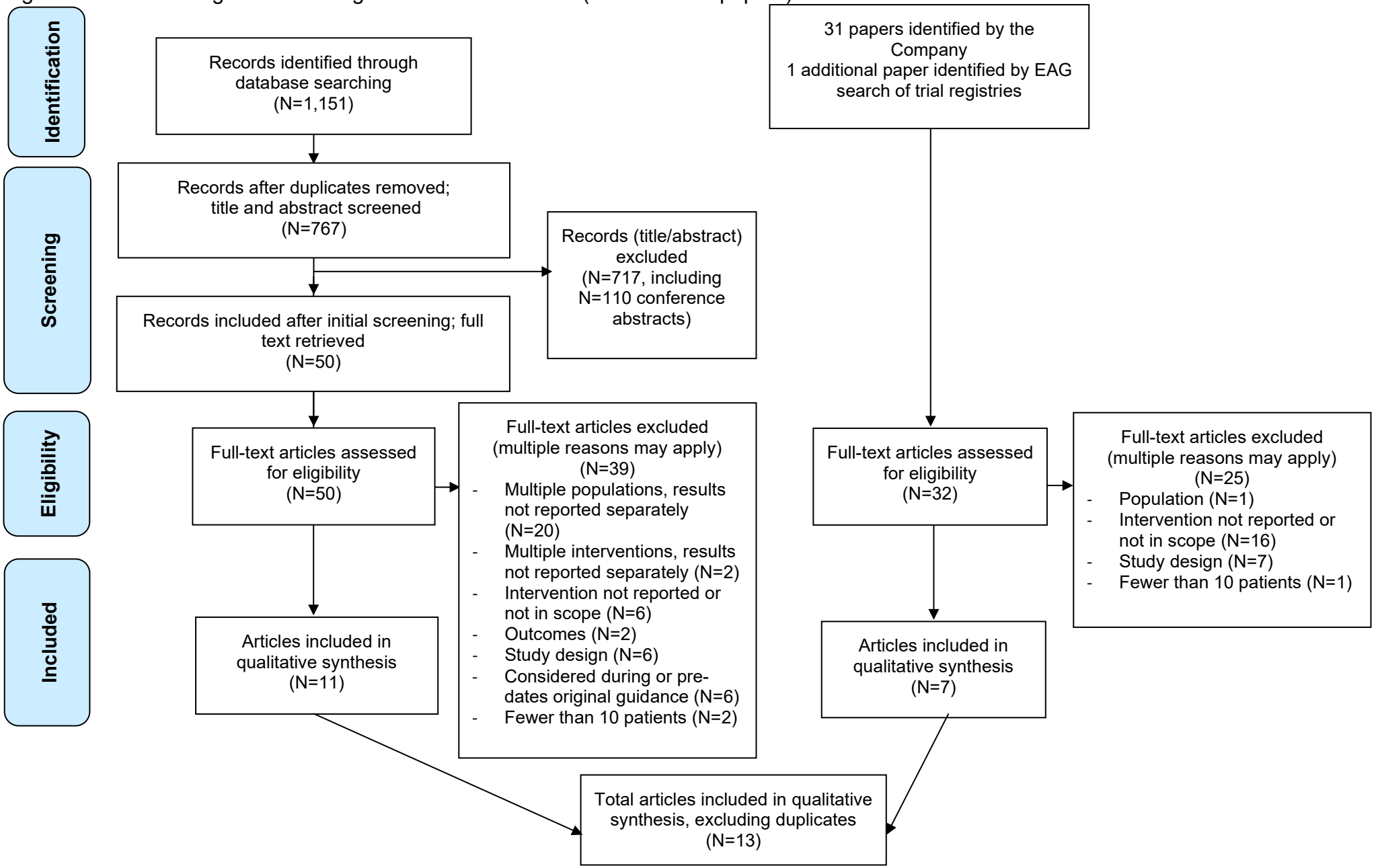
NICE Information Services (IS) repeated the original search strategy used for MTG41, with revised dates (June 2017 to May 2022). The IS search identified 1,151 references, reduced to 767 references after deduplication, and shared a reference library with the EAG. The 767 titles and abstracts were sifted and checked by two reviewers (RO and KK). With agreement from NICE, the EAG excluded 110 conference abstracts at this stage, on the basis of the volume of evidence found, the likelihood that they would be of low quality, and the potential for them to be duplicates of subsequently published full text articles. However, the EAG notes that although in scope, the original Company submission excluded patients with upper limb pain due to a lack of evidence, and focused only on back and leg pain. The EAG has therefore applied this same restriction to this review of the evidence, excluding 28 references at the first sift. The full text articles for the remaining 50 papers were retrieved and assessed for inclusion against the scope (NICE MTG41 Scope, 2017) by a single reviewer (RO). A total of 39 were excluded from this search on full text review (Appendix C). This included two papers which, although in scope for this review, were already considered by the Medical Technology Advisory Committee (MTAC) during consultation (De Andres et al. 2017, Al-Kaisy et al. 2018). This also included Al-Kaisy *et al*. (2019), Al-Kaisy *et al*. (2020), and Amirdelfan *et al*. (2018), which reported on subgroups from two studies included in the original Assessment Report (SENZA-RCT: Kapural *et al*. 2015, Kapural *et al*. 2016a, Kapural *et al*. 2016b, and Kapural *et al*. 2016c; SENZA-EU: Al-Kaisy *et al*. 2014 and Van Buyten *et al*. 2013). These three papers gave no extended follow up data, results for additional outcomes, or results for specific subgroups relevant to the scope, and have therefore been excluded to avoid double-counting the included patients. To remain consistent with the original Assessment Report, the EAG also excluded studies reporting on fewer than ten patients.

A paper by D'Souza *et al.* (2022), reporting exclusively on adverse events, has been included under Section 4.7: other relevant information, but otherwise excluded.

Two additional papers were identified for inclusion: one provided by the Company (Abraham *et al.* 2021), and the other found by the EAG (Peterson *et al.* 2022b; published after the date of the NICE IS search). Of the 31 papers provided by the Company, 18 of these were also identified by the NICE IS search. Reference lists of identified systematic reviews were also hand-searched by a single reviewer (RO), but no further papers were identified in this way. A total of 13 papers, reporting on 11 studies, remained for inclusion.

A summary of the sifting and selection process of the EAG literature search is reported in Figure 1.

Figure 1: PRISMA diagram illustrating EAG literature search (N: number of papers)



The EAG categorised the outcomes of interest defined in the final scope into:

- efficacy (pain, duration of pain relief, patient satisfaction, health related quality of life, functional disability, opioid and other analgesic use) and
- safety (device-related adverse events, implantation time in theatre, incidence of paraesthesia, implant lifetime, reason for implant removal, follow-up appointments, staff conducting device programming).

Where the Peterson *et al*. papers (2021, 2022a and 2022b) report results from the same patients for the same outcomes, the paper with the longest follow up, or most complete reporting, has been selected for inclusion.

The Instructions for Use for Senza state only that the device is contraindicated in those who have not had a successful trial. As trial success was also included in the economic model for Senza, the EAG also tabulated this additional outcome for all included studies.

4. New evidence

4.1 Changes in technology

The Company confirmed that both Senza and Senza II have been superseded by Senza Omnia, which is available to the NHS. The technical specifications have not changed, and it is covered by the existing CE mark. The Company reported that Senza Omnia has additional digital functions which may provide additional benefits to patients and healthcare providers, in terms of handling and ease of use, and more versatile and flexible treatment options. The Company confirmed that Senza is the only device capable of delivering 10 kHz SCS therapy, that all Senza devices can also deliver low frequency (between 2 Hz and 1,200 Hz) SCS therapy, and that these can be delivered independently or in combination. This may give an alternative option if high-frequency therapy does not achieve a reduction in pain; however will depend on the location of the pain, and placement of the Senza leads. The Clinical Experts confirmed that they place the leads for Senza anatomically, that is, without mapping the paraesthesia generated by low frequency treatment to

the areas of pain. This means that switching from high to low frequency treatment may not be effective if the lead placement does not provide stimulation to cover the areas needed, although one Clinical Expert said that paraesthesia mapping was not needed to be able to use Senza at low frequency after anatomical placement. One Clinical Expert reported that between 10% and 20% of patients with a high frequency device may need a low frequency waveform, and another Clinical Expert reported that in their practice, less than 1% would be using Senza at a low frequency. Two Clinical Experts also confirmed that the high and low frequencies can be combined in a single treatment program, and that up to five programs may be set up in clinic. The patient receives a handheld remote to switch between the programs, to adjust the stimulation given, depending on the pain relief they need. Clinical Experts also said that Senza Omnia has an improved recharging system, and the Company confirmed that this did not affect use of the device.

4.2 Changes in care pathways

The EAG has reviewed the clinical guidance (Appendix A) and found no significant updates in care pathways relevant to Senza.

Clinical Experts confirmed the care pathway relating to Senza has not changed since MTG41 was published. However, two Clinical Experts advised that Senza has now been trialled in people with painful diabetic neuropathy, and is currently being used within this patient group. One Clinical Expert advised that Senza would be used if pain relief was not achieved with a trial of conventional low frequency SCS. Another Clinical Expert said it is being used as a 'salvage' therapy for people who had a successful trial of low-frequency SCS, which then became less effective over time, highlighting the value of long term study follow up. One Clinical Expert advised that an increased awareness of Senza HF10 has led to increased uptake of the device.

One Clinical Expert said that more centres are becoming convinced that high frequency SCS is better than conventional low frequency, or newer low frequency waveform, treatments for back and leg pain. They estimated that

more than 50% of SCS devices implanted in the UK are now Senza.

One Clinical Expert noted a change in terminology from failed back surgery syndrome (FBSS) to persistent spinal pain syndrome (PSPS), which has two types: type I (chronic pain without prior back surgery), and type II (chronic pain following back surgery). This change is expected to be made across the NHS when the International Classification of Diseases 11th edition (ICD-11) is introduced, but is already in use in at least one trust. This change is intended to address stigmatisation of people with chronic non-surgical neuropathic back and limb pain and to better inform treatment.

The EAG was unable to identify any competing SCS devices which could deliver high frequency therapy. The EAG did identify several comparator devices (for example those manufactured by Medtronic, Abbott, Boston Scientific, StimWave Technologies) that offer lower frequency stimulation, and these were verified by the Clinical Experts (Appendix G2).

The Clinical Experts were not aware of any adverse events or safety issues that would not have been identified by MHRA or FDA MAUDE searches.

The EAG notes that an RCT (n=105) by Eldabe *et al*. (2020) found no difference in outcomes between patients undergoing trial stimulation (using various SCS devices), and those proceeding straight to permanent implant, across three UK centres. A recently published follow-up to this (Duarte *et al*. 2022), found that such an approach could save the NHS £500,000 a year from 2023/24 onwards. Proceeding straight to permanent implantation (and not including an initial trial with the device) will have future implications on the care pathway for patients being treated with spinal cord stimulation and a cost implication for Senza and conventional SCS devices.

4.3 Results from the MTEP research commissioning workstream

Due to the positive recommendation of MTG41, the NICE Medical Technologies Evaluation Programme (MTEP) did not commission any further research to inform the guidance review.

4.4 New studies

A total of 13 papers (including 3 by Peterson *et al*. [2021, 2022a, 2022b] reporting on the same study) were included in this evidence review, which included 1 economic study (Taylor *et al.* 2020). The remaining 10 clinical studies (12 papers, Appendix D) included:

- Two RCTs, considered by the EAG as single-arm cohort studies, because the comparator (conventional medical management [CMM]) was not in line with the scope: one reported in Kapural *et al*. 2022; one reported in Peterson *et al*. 2021, Peterson *et al*. 2022a, and Peterson *et al*. 2022b;

- One case-control study, considered by the EAG as a single-arm cohort study, because the comparator (CMM) was not in line with the scope (DiBenedetto *et al*. 2018);

- Seven cohort (single-arm) studies, including four retrospective studies (Chen *et al*. 2022, Sayed *et al*. 2020, Torres-Bayona *et al*. 2021, Abraham *et al*. 2021), and three prospective studies (Cordero Tous *et al*. 2021, Kallewaard *et al*. 2021, De Groote *et al*. 2020).

The 10 included clinical studies (excluding the economic study by Taylor *et al*. 2020) reported on a total of 515 patients receiving Senza as an intervention, ranging in size from 11 (De Groote *et al*. 2020) to 113 (Peterson *et al*. 2021, Peterson *et al*. 2022a, Peterson *et al*. 2022b) patients, Table 1.

Studies included a range of patient subgroups:

- Four studies included patients with failed back surgery syndrome (Kallewaard *et al*. 2021, De Groote *et al*. 2020, Abraham *et al*. 2021, Torres-Bayona *et al*. 2021). The population reported in Abraham *et al*.

(2021) also had sciatica, and the population reported in Torres-Bayona *et al*. (2021) also had neuropathic lower limb pain;

- Three included patients with back pain (Kapural *et al*. 2022 reported the back pain as non-surgical; Sayed *et al*. 2020 and DiBenedetto *et al*. 2018 did not define the origin of back pain). DiBenedetto *et al*. (2018) reported their population as being with or without leg pain;

- One included patients from two populations: complex regional pain syndrome and failed back surgery syndrome (Cordero Tous *et al*. 2021);

- Two included patients with diabetic neuropathy (Chen *et al*. 2022, one reported in Peterson *et al*. 2021, Peterson *et al*. 2022a, and Peterson *et al*. 2022b).

The studies and patient populations included in the evidence were heterogeneous in nature. A variety of prior treatments before using Senza were reported, including: physical rehabilitation, opioid and non-opioid analgesics, and invasive therapies (local facet joint or medial branch anaesthetic, nerve block, neuroaxial block, radiofrequency epidural adhesiolysis). These prior treatments may not reflect UK NHS practice, and may not align with the recommendation in NICE TA159 that patients have undergone at least six months of conventional medical management before being treated with SCS. One study explicitly reported use of unsuccessful conventional spinal cord stimulation prior to use of Senza, three studies explicitly excluded patients with prior or existing SCS devices, and eight did not report on prior treatments within their eligibility criteria.

All included studies reported pain scores. However, the EAG is unable to summarise trends due to the large variation in reporting across included studies. Scoring systems to measure pain at baseline varied across studies, with some studies using multiple measures.

The baseline pain level varied across studies (for example, mean VAS on a 10 cm scale between 3.30 cm and 8.52 cm, across 6 papers), with difference

in type of pain (back, leg, back and leg), and pain measured at different follow-up time points (baseline, end of SCS trial, 1, 3, 6, 12), reporting numerical or proportionate change in pain score. The EAG notes that pain scores are not collected in the UK Neuromodulation Registry (4.5 UK Neuromodulation Registry).

A range of quality of life tools (for example, EuroQol five Dimensional Questionnaire, EQ-5D; Short Form Health Survey, SF-36; Medical Outcomes Study Sleep Scale, MOS-SS; HAD, Hospital Anxiety and Depression scale) and functional disability measures (for example, Functional Rating Index, FRI; Oswestry Disability Index, ODI; Global Assessment of Functioning, GAF) were also reported across studies at different follow-up time points. This variation in reporting, reflecting the heterogeneity across the single arm studies, meant that meta-analysis was inappropriate. The EAG notes that quality of life measures collected in the UK Neuromodulation Registry include EQ-5D and occupational status (4.5 UK Neuromodulation Registry).

Table 1: Cross tabulation of included studies against outcomes

			Efficacy							Safety						
Author (year); Country	Study design (number of patients)	Population	Successful device trial	Pain scores	Duration of pain relief	Patient satisfaction	Health related QoL	Functional disability and improvement	Opioid and other analgesic use	Device-related adverse events	Implantation time in theatre	Incidence of paraesthesia	Implant lifetime	Reason for implant removal or revision	Follow up appointments	Staff conducting device programming
Kallewaard *et al.* (2021); Netherlands	Prospective cohort (n=68)	FBSS with predominant back pain	☑	☑		☑	☑	☑	☑	☑						
Cordero Tous *et al.* (2021); US	Prospective cohort (n=18)	FBSS or complex regional pain syndrome	☑	☑	☑	☑		☑	☑	☑						
De Groote *et al.* (2020) Belgium	Prospective cohort (n=11)	FBSS	☑	☑			☑									
Torres-Bayona *et al.* (2021); Colombia	Retrospective cohort (n=62)	FBSS and neuropathic lower limb pain	☑	☑						☑		☑		☑		
Abraham *et al.* (2021) US	Retrospective cohort (n=21)	FBSS and sciatica		☑	☑		☑	☑	☑	☑						
Kapural *et al.* (2022); US	Cross-over RCT* (n=159, n=82 in intervention arm)	Non-surgical chronic low back pain	☑	☑		☑	☑	☑	☑	☑				☑		
DiBenedetto *et al.* (2018); US	Retrospective cohort (n=32)	Chronic back pain, with or without leg pain		☑	☑			☑	☑						☑	
Sayed *et al.* (2020); US	Retrospective cohort (n=19)	Thoracic back pain	☑	☑	☑		☑	☑	☑	☑						
Peterson *et al.* (2022a) US	Cross-over RCT* (n=216, n=113 in intervention arm)	Painful diabetic neuropathy	☑	☑	☑		☑			☑				☑		
Peterson *et al.* (2021) US	Cross-over RCT* (n=216, n=113 in intervention arm)	Painful diabetic neuropathy	☑	☑		☑	☑	☑		☑		☑				
Peterson *et al.* (2022b) US	Cross-over RCT* (n=216, n=113 in intervention arm)	Painful diabetic neuropathy	☑	☑	☑	☑	☑			☑				☑		
Chen *et al.* (2022); US	Retrospective cohort (n=89)	Painful diabetic neuropathy		☑	☑		☑	☑					☑	☑		

Key: *Studies treated as single arm as comparator is out of scope

Abbreviations: FBSS, failed back surgery syndrome; RCT, randomised controlled trial; QoL, quality of life

Trial outcome

A total of 7 studies reported on the proportion of patients undergoing a successful trial ranging from 61% to 100%, Table 2. However, the trial duration reported across these studies ranged between 5 days and 4 weeks, and the definition of trial success also varied. The Instructions for Use for Senza state only that the device is contraindicated in those who have not had a successful trial, but do not explicitly state the duration of trial period, nor define what is deemed as a successful trial outcome. The EAG has considered successful trials only according to the definition reported for each study, and notes that not all patients may have gone on to permanent implantation or completed follow up, because of adverse events, patient preference, or other factors.

Table 2: Summary of 7 papers reporting on successful trial outcome, as defined by authors

Author (year)	Pain location	Trial success definition	Successful trial (intervention device)
Cordero Tous *et al*. (2021)	Back	At least 3 programs over 2 weeks, proceeded to implant if improvement of the previous condition by 50% or more was achieved (unclear if VAS)	61% (11/18)
De Groote *et al*. (2020)	Back	4 week trial, pain reduction of at least 50%, and reduction in pain medication of at least 50% needed for permanent implant	100% (11/11)
Kallewaard *et al.* (2021)	Back	7 to 21 day trial, patients who experienced ≥ 50% reduction in baseline leg pain (VAS) proceeded to permanent implant	88% (60/68)
Kapural *et al*. (2022)	Back	Up to 14 day trial, success defined as ≥50% pain relief	92.5% (74/80) [Within the CMM arm: 86.7% (65/75) elected to crossover to intervention arm, with 93.8% (61/65) success]
Sayed *et al*. (2020)	Back	5 to 10 day trial, with success defined as ≥50% pain relief over the course of the trial (VAS)	89.5% (17/19)
Peterson *et al*. (2022b)	Leg	1 to 2 week trial, patients with relief of ≥50% in VAS eligible for permanent implant Note, Peterson *et al*. (2021) reported trial length as 5 to 7 days.	94.2% (98/104) [Within the CMM arm: 81% (77/95) elected to crossover from comparator arm to intervention arm, with 97.4% (75/77) success]

Author (year)	Pain location	Trial success definition	Successful trial (intervention device)
Torres-Bayona *et al*. (2021)	Leg	7 to 10 day trial, clinical response defined as having 50% or greater pain reduction with no stimulation-related neurological deficit	95.9% (70/73)
Abbreviations: CMM, conventional medical management; NRS; Numerical Rating Scale; SCS spinal cord stimulation; VAS, Visual Analogue Scale;			

Pain scores and duration of pain relief

Eleven single arm studies reported on the numerical or proportionate change in pain scores following Senza implantation, all of which classified patients as being in response or in remission based on an applied threshold to the change in pain score at follow-up (Appendix E1a-d). The EAG notes that a statistically significant reduction in back and leg pain scores were observed up to 12 months in 5 studies (Abraham *et al*. 2021, Sayed *et al*. 2020, Cordero Tous *et al*. 2021, DiBenedetto *et al*. 2018, and Peterson *et al*. 2022a and Peterson *et al*. 2022b reporting on the same study). Peterson *et al*. (2022b) also reported a statistically significant percentage reduction in pain at 6 and 12 months. Chen *et al*. (2022) reported pain outcomes at 24 months, with 88.9% (24/27) of patients still reporting at least 50% pain relief. However, the EAG notes that only 27 of the 73 included patients had follow up data available at this time point.

Patient satisfaction

Patient Global Impression of Improvement or Patient Global Impression of Change

Four single arm studies reported on Patient Global Impression of Change, with between 54% and 73% of patients reporting that their pain had improved "much" or "very much" at 12 months when compared with baseline (Appendix E2).

Patient reported satisfaction

Four single arm studies also reported on patient satisfaction (Appendix E2). Cordero Tous *et al*. (2021) found that all patients reported a high degree of satisfaction with the treatment. Peterson *et al*. (2021, 2022a, and 2022b) gave patients the option to crossover to the other treatment arm at 6 months if they achieved less than 50% pain relief, were dissatisfied with current treatment, and the investigator agreed that changing treatment was appropriate. None of the patients in the intervention arm crossed over.

Health-related quality of life

Four single arm studies also reported quality of life measures up to 12 months (Appendix E3). Statistically significant improvements in components of the EQ-5D were reported in one study at 6 and 12 months (Peterson *et al*. 2022b, reporting EQ-5D-5L VAS and EQ-5D-5L index score), when compared with baseline. Peterson *et al*. (2022b) also reported statistically significant improvements in all reported domains on the Diabetes Quality of Life instrument at 6 and 12 months. However due to the variability in tools used, at different follow-up time points, across different subgroups, and lack of comparator arm, the EAG is unable to use these results to draw conclusions regarding efficacy.

Functional disability measures

Five single arm studies reported functional disability measures up to 12 months (Appendix E4). Cordero Tous *et al*. (2021) reported the most significant (assumed by the EAG to be clinical significance, and not statistical

significance, as no p-values reported) improvement in the “sleeping” and “walking” components of the Functional Rating Index, at 12 months, when compared with baseline. DiBenedetto *et al*. (2018) reported significant improvement on the modified Roland Morris Disability Questionnaire, also at 12 months, when compared with baseline. However due to the variability in tools used, at different follow-up time points, across different subgroups, and lack of comparator arm, the EAG is unable to use these results to draw conclusions regarding efficacy.

Opioid and other analgesic use

No comparative evidence reported on opioid use between Senza and conventional SCS. Seven single arm studies reported on opioid use, Appendix E5. Decreased opioid or analgesic use was reported in between 7.0% (Kallewaard *et al*. 2021) and 71.4% (DiBenedetto *et al*. 2018) of patients, and discontinued use was reported in between 21.9% (Kapural *et al*. 2022) and 36.0% (Cordero Tous *et al*. 2021) of patients. Between 6.0% (Kapural *et al*. 2022) and 9.0% (Cordero Tous *et al*. 2021) of patients had increased doses of opioids or analgesics over the course of the study. The EAG notes inconsistent, incomplete or likely incorrect reporting in two of the included studies (Cordero Tous *et al*. 2021, Kallewaard *et al*. 2021), and the results should therefore be interpreted with caution.

Device-related adverse events

The EAG has summarised adverse events leading to surgical revision, relocation or complete explantation under the “Reason for implant removal (or revision)” outcome.

No adverse events

Cordero Tous *et al*. (2021) and Sayed *et al*. (2020) reported no serious adverse events, but did not provide a definition for this. Although Kallewaard *et al*. (2021) reported 6 serious adverse events, in 5 patients, none were unanticipated, and all resolved. Abraham *et al*. (2021) also reported no complications or adverse events, and Torres-Bayona *et al*. (2021) reported no procedure-related mortality.

Infection

Torres-Bayona *et al*. (2021) reported one infection treated with antibiotics. Kapural *et al*. (2022) reported mild or moderate implant site infections in five patients. Peterson *et al*. (2022a) reported three infections that were treated conservatively and resolved, allowing the patient to continue in the study.

Pain

Implant site pain or discomfort, without revision, was reported by Kapural *et al*. (2022) in four patients, and by Peterson *et al*. (2021) in one patient. Incision site pain was reported by Peterson *et al*. (2021) in one patient.

Neurologic deficits

Peterson *et al*. (2021, 2022b) reported there were no neurologic deficits related to the stimulation provided, although Peterson *et al*. (2021) reported one case of hyporeflexia. Kapural *et al*. (2022) reported one patient with neurological deficit at three months, resolved by adjusting the stimulation.

Other adverse events

Kapural *et al*. (2022) reported three cases of transient cerebrospinal fluid leakage. Peterson *et al*. (2021) reported two cases of wound dehiscence, and one each of impaired wound healing, device extrusion, contact dermatitis, urticaria, radiculopathy, gastroesophageal reflux, myalgia, and arthralgia.

Reason for implant removal (or revision)

Removal or revision due to adverse events

Torres-Bayona *et al*. (2021) reported six revisions: three for lead migration, two for infection, and one for skin erosion at the implant site. Kapural *et al*. (2022) reported three revisions for lead migration, two patients who had their device explanted and reimplanted because of infection, and two with their devices repositioned because of implant site pain. Peterson *et al*. (2022b) reported one revision because of lead migration, five patients with infections treated with surgical explantation, one of which was reimplanted, and two who had their IPG location revised. Chen *et al*. (2022) reported that one patient

with a permanent implant was not included in the analysis because they had pocket site pain and were awaiting explantation.

Removal due to loss of efficacy

Peterson et al. (2022b), and Kapural *et al*. (2022) reported that no patients had devices explanted because of efficacy, although Kapural *et al*. (2022) reported two revisions for this reason. Torres-Bayona *et al*. (2021) reported that treatment was unsuccessful in 22% (14/62) of patients after successful trial, and in two of these, stimulation was never effective after implantation. It was not reported whether these devices were explanted. Chen *et al*. (2022) reported that six patients with permanent implants, after successful trials, were excluded from analysis because of lack of pain relief and were awaiting explantation. Average time with the device before explant was reported as 25.9 months, but this includes explantation for other reasons, such as pain.

Implantation time in theatre

None of the included studies reported on this outcome.

Incidence of paraesthesia

Two single arm studies reported on paraesthesia as an outcome. Torres-Bayona *et al*. (2021) reported that pain relief occurred in the absence of paraesthesia for patients with successful trials. However, the trial failed for one patient who had incomplete coverage and an unpleasant sensation. Peterson *et al*. (2021) reported that one patient experienced uncomfortable stimulation, but did not explicitly refer to this as paraesthesia.

Implant lifetime

None of the included studies reported on implant lifetime. Chen *et al*. (2022) reported that two patients included in the analysis had their devices “inactive”, but it is not clear to the EAG whether this refers to a device failure, or a loss of efficacy and stopped treatment.

Follow-up appointments

The study by DiBenedetto *et al.* (2018) reported no difference in the mean number of hospital visits between 12 month follow-up and baseline. A statistical difference in mean number of procedures at 12 month follow-up

compared with baseline was reported (0.7 vs. 2.5, p<0.001), equivalent to a 72% reduction in the use of interventional procedures; however the EAG notes that this study included only 32 patients treated with Senza.

Staff conducting device programming
None of the included studies reported on this outcome.

4.5 UK Neuromodulation Registry

The EAG met with the UK Neuromodulation Registry on 12 September 2022 to determine the quantity and quality of data relating to Senza, submitted to the registry following publication of the NICE MTG41 guidance (and its recommendations which stated clinicians implanting Senza should submit timely and complete data to the UK Neuromodulation Registry), Appendix G3. They estimated that there are around ten large implanting centres in the UK, and there are smaller centres implanting only around 10 to 15 devices a year. Overall, they estimated around 60% of centres are entering their neuromodulation data into the registry, but noted that this is across all SCS devices, and not just Senza. The EAG asked about the outcomes relevant to this review, and they indicated that they recorded whether a trial had taken place or not, but that this is not mandatory so reporting is not complete. Trial efficacy data is not collected. They also noted delays in some centres between successful trial and permanent implant, with some waiting as long as 9 months, and stated that some centres no longer offer trials and move straight to permanent implantation, in line with the findings of Eldabe *et al.* (2020) and Duarte *et al.* 2022. The EAG notes that trial efficacy was included in the economic model which led to guidance development.

Opioid usage is not recorded in the registry. The registry focuses on quality of life measures (including EQ-5D and occupational status), rather than pain measures (for example, VAS), and future developments will include a mobile phone app, and ability for patients to record Patient Reported Outcome Measures Information System 29 (PROMIS 29) scores. The EAG notes that the economic model used to support guidance development is dependent upon the proportion of patients achieving optimal pain relief, and not quality of life measures.

In terms of safety, revision data is not well completed in the registry and is further skewed by inconsistent recording of devices being explanted. Routine administrative databases may also be of limited value, as some hospitals apply clinical coding for an explantation to reflect the removal of the device at the end of a trial.

After the meeting, the UK Neuromodulation Registry were able to provide a brief summary of data from the registry relating to neuromodulation procedures, and more specifically, Senza. They reported that about 35 centres perform neuromodulation procedures in the UK, that 29 of them are registered with the UK Neuromodulation Registry, and that 24 are submitting SCS data. Of these [redacted] enter data relating to Senza devices. There are [redacted] Senza implants currently registered, and [redacted] of these are in populations relevant to the scope, with back or lower limb pain. There are currently [redacted] implants recorded with at least 12 months of follow up. Data completeness was also reported, with gender being entered in [redacted]% of cases, date of birth in [redacted]%, IPG manufacturer in [redacted]%, model in [redacted]% and device serial number in [redacted] Quality of life, using the EQ-5D, is recorded pre-operatively in [redacted]% of cases. Data relating to adverse events is not available, and pain scores (for example, using VAS) are not recorded.

The UK Neuromodulation Registry is intending to publish reports of the data it holds at the end of September 2022, which will include all SCS devices, and will not identify specific manufacturers. Device specific reports will be shared directly with the manufacturers. The EAG would recommend that NICE request the report for Senza directly from the manufacturer (Nevro).

A Clinical Expert from the Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) has shared (15 September 2022) a high-level summary of unpublished data from an ongoing service evaluation of 20 patients using Senza device by Nevro for mixed indication for pain (that is not restricted to back and lower limb pain). NuTH also contributes to a local database of neuromodulation patients, not exclusively with Senza, which have not yet been submitted to the UK Neuromodulation Registry. This dataset has shown trial success in more than 80% of patients, and low rates of infection, lead migration and explantation associated with Senza.

The EAG has also been provided with summary data from Leeds Teaching Hospitals NHS Trust (15 September 2022). They reported 475 Senza implants since 2012, with trial stimulation used before permanent implantation up to 2020, and around 50 trial failures recorded. Nearly 80% have pre- and post-implantation pain on VAS recorded, and quality of life is measured, using the EQ-5D, both before and after implant.

4.6 Ongoing trials

The EAG searched for "Nevro OR Senza" on 17 August 2022 and identified six studies; two are recruiting, two are active but not recruiting and two have unknown status, Appendix F. The EAG also identified one additional study which terminated due to limited enrolment having only recruited three patients (NCT04020211; HF10 Treatment of Chronic Knee Pain).

4.6 Changes in cost case

The Company has confirmed that the cost of the technology has not changed since the original guidance.

The EAG has identified one additional economic study published by the Company following the original guidance (Taylor *et al.* 2020). This economic study used the exact same model structure and model parameters previously reviewed during the EAG Assessment Report (2019), however with added utility values and cost-effectiveness analysis. The study reported that 10 kHz spinal cord stimulation (SCS) was cost-saving and cost-effective when compared with low-frequency non-rechargeable (mean savings, £7,170 [95% CI £6,767 to £7,573] per patient) and rechargeable (mean savings, £3,352 [£3,313 to £3,792] per patient) spinal cord stimulation devices. The study found that 10 kHz-SCS had 95% likelihood of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY. The authors acknowledged the lack of real-world data beyond two years, such that long-term device and battery longevity were uncertain; but that the device lifespan of 10 kHz-SCS could be reduced from ten years to six years and remain cost saving. The authors also noted that their economic model did not account for three benefits of 10 kHz-SCS when compared to low-frequency SCS: 1) the

improvement in the continuity of pain reduction and improvement of Health-Related Quality of Life, 2) avoidance of paraesthesia mapping during implantation of the device therefore short procedure times, and 3) a reduction in concomitant opioid use.

The clinical parameters used within Taylor *et al.* (2020) are described in Table 7, and are in agreement with the original economic model reviewed during the Assessment Report.

Table 7: Summary of clinical parameters used within Taylor et al. 2020 and MTG41 published in 2019.

Clinical parameter	Original value (MTG41, 2019)				EAG comment
	CMM	HF10-SCS +CMM	TNR-SCS +CMM	TR-SCS +CMM	
Trial success	N/A	92.8%	88.0%	88.0%	Same values used in Taylor *et al.* 2020. The EAG would note that there is evidence of centres no longer including a trial phase. This would apply to both intervention and comparator arm and therefore the point estimates in both arms would reduce. Due to the removal of the trial phase, the number of devices explanted (due to lack of reduction in pain) may increase in both Senza and conventional SCS arms.
Optimal pain relief (short term)	9.3%	80.9%	54.4%	54.4%	Same values used in Taylor *et al.* 2020.
Short-term complications	0%	33.7%	35.8%	35.8%	Same values used in Taylor *et al.* 2020.
Long-term complications	0%	3.7%	12.0%	12.0%	Same values used in Taylor *et al.* 2020.
Explant - year 1 - year 2 - year 3+	N/A	 4.4% 4.7% 3.2%	 11.1% 9.7% 3.2%	 11.1% 9.7% 3.2%	Same values used in Taylor *et al.* 2020. As stated above, due to some centres not including a trial phase, the explant rate may increase (due to lack of reduction in pain); but would increase in both Senza and conventional SCS arm.
Device longevity, years	N/A	10	10	4	Same values used in Taylor *et al.* 2020.
Proportion of patients receiving another reoperation	5.0%				Same values used in Taylor *et al.* 2020.
Optimal pain relief (long term)	19.0%				Same values used in Taylor *et al.* 2020.

Clinical parameter	Original value (MTG41, 2019)				EAG comment
	CMM	HF10-SCS +CMM	TNR-SCS +CMM	TR-SCS +CMM	
Annual death	0.81%				Assumed independent of health state. Same values used in Taylor *et al.* 2020.
Abbreviations: CMM, conventional medical management; N/A, not applicable; SCS, spinal cord stimulation; TNR, traditional low-frequency non-rechargeable; TR, traditional low frequency rechargeable;					

The EAG notes that there is evidence of UK NHS centres no longer including a trial phase. This would apply to both intervention and comparator arm and therefore the point estimates in both arms would reduce. Due to the removal of the trial phase, the number of devices explanted (due to lack of reduction in pain) may increase in both Senza and conventional SCS arms. However, the impact of removing the trial phase on clinical and economic outcomes is uncertain.

4.7 Other relevant information

The study by D'Souza *et al.* (2022) summarised 1,651 reports to the Manufacturer and User Facility Device Experience (MAUDE) submitted between 01 January 2016 and 31 December 2020 which were specific to 'Nevro' and product code 'LGW' (which includes Stimulator, Spinal-Cord, Totally Implanted For Pain Relief, which the authors claim uniquely identified the dorsal column SCS devices that deliver 10kHz stimulation). The study reported that the majority of entries were categorised as procedural complications (72.6%, n=1,198), followed by serious adverse events (10.5%, n=174), device-related complications (10.5%, n=173) and patient complaints (9.9%, n=164); with multiple categories being assigned in some cases.

- The most common procedural complications were non-neuraxial infection (52.9% n=634), new neurological symptoms (14.7% n=176) and dural puncture (9.5% n=114).
- The most common device-related complications were lead damage (41.6% n=72), erosion (18.5% n=32) and difficult insertion (11.5% n=20). Other device-related complications included migration (8.1% n=14), hardware malfunction (6.9% n=12), anchor damage (6.4%

n=11), reaction to the device (4.0% n=7) and difficult lead removal (2.9% n=5).

- The most common patient complaints were non-incisional pain (50.6%, n=83), IPG pain (18.9% n=31) and unwanted stimulation (10.4% n=17).
- Most complications were managed surgically through explantation (50.9%, n=840) rather than revision (5.0%, n=82) or incision or drainage (6.6%, n=109).

D'Souza *et al.* (2022) acknowledged that MAUDE is a passive surveillance system which may be subject to incomplete, incorrect, unverified and biased data. However, they also highlighted that the data may be used to inform clinical decisions associated with 10kHz spinal cord stimulation.

The EAG notes that an additional 946 MAUDE reports have been submitted between 01 January 2021 and 31 July 2022 using the same approach, or an additional 936 when searching 'Nevro' and 'Senza', Table 8. The event type for the 936 reports included 666 injuries, 245 deaths, and 25 malfunctions.

Table 8: Results from MAUDE (search conducted by EAG 16 August 2022).

Date period	Manufacturer: Nevro Brand name: Senza	Manufacturer: Nevro Product Class: LGW
01/01/2021-30/06/2021	241	242
01/07/2021-31/12/2021	340	347
01/01/2022-31/07/2022	355	357
TOTAL	**936**	**946**

The EAG note that these MAUDE reports are related to all indications of use for Nevro Senza device (and are not restricted to chronic neuropathic back and lower limb pain in line with the scope of this MTG41 evidence review). The EAG also notes that the events identified may not have been directly related to Senza, for example, a report may have been to MAUDE for a patient with a device implanted who subsequently died, but the device itself may not have been the cause of death. The EAG notes that a large proportion of MAUDE reports had insufficient or missing information. Additionally, the

EAG is unable to put the number of MAUDE reports into context due to the lack of implantation data (the denominator is unknown).

The EAG conducted a search of MHRA database on the 18 August 2022 using terms; “Nevro”, “Senza”, and identified one MHRA field safety notice issued on 30 April 2021, relating to incorrect MRI safety labelling (patients were given an incorrect implant/patient ID card that stated “MR conditional” when the device should have been identified as “MR unsafe”).

The EAG contacted the UK Neuromodulation Registry to determine how widely Senza is used, and how frequently adverse events are known to have occurred in a UK NHS setting. They are expected to publish a report of their data in September 2022. However, it is expected that any data available will be limited to revision procedures, which are not entered fully by all centres, and may not include the reasons for revision. The EAG has received limited information from a local expert, who reported low rates of infection, migration and revision.

5. Conclusion

Overall, there is a lack of robust and publicly available UK data relating to Senza, particularly, a lack of evidence comparing Senza with conventional SCS. There is nothing in the published evidence identified that would support a change to the existing guidance recommendations.

The EAG identified a total of 10 single arm clinical studies (12 papers) published since MTG41, which included a total of 515 patients treated with Senza. However, none of the newly identified evidence compared treatment with Senza with treatment with conventional SCS, in line with the Final Scope. Therefore, none of the new evidence goes against or supports the previous recommendation that Senza is “at least as effective as low-frequency SCS”. The included single-arm studies generally reported that treatment with Senza reduced pain, and improved quality of life and functional measures, at time points up to 12 months. Three papers published since the original guidance

(all from the same study) included conventional medical management as a comparator, but were conducted in the US, where medical management may not be generalizable to the UK. Furthermore, as the literature search was focused on Senza, it was not possible for the EAG to conduct an indirect comparison with conventional SCS (when compared against conventional medical management), where the evidence base may have also been updated. Evidence from the UK is lacking. The original guidance recommended that "clinicians implanting SCS devices including Senza should submit timely and complete data to the UK Neuromodulation Registry", and relevant data are expected to be published by the UK Neuromodulation Registry later this month (September 2022) including approximately 720 Senza patients. This Real-World Evidence may demonstrate whether the benefits of Senza are realised in a UK NHS setting.

There were 3 studies (Kapural *et al*. 2022, DiBenedetto *et al*. 2018, and Sayed *et al*. 2020) reporting on a population with back pain, without failed back surgery. Only two single arm studies reported on patients with painful diabetic neuropathy (Chen *et al*. 2022; Peterson *et al*. 2021, 2022a, and 2022b). For each of these populations, results were consistent with the overall evidence base, reporting reduced pain, and improved quality of life and functional measures, at time points up to 24 months (Chen *et al*. 2022) for patients with painful diabetic neuropathy. Whilst Senza may continue to be considered in these patient groups (in line with the original guidance recommendations), the EAG has not identified any comparative evidence in these subgroups (back pain without failed back surgery, or painful diabetic neuropathy), and is unable to comment on the effectiveness or safety of Senza when compared with conventional spinal cord stimulation in these specific patient groups.

There is a wide range of SCS trial success (prior to permanent implantation) between 61% and 100% as identified from 7 studies, which highlights the importance of robust patient selection. However, the EAG has identified evidence to suggest that some NHS centres no longer conduct a trial with the spinal cord stimulation devices, and instead proceed straight to permanent

implantation. Given the paucity of data from published UK studies, this change may impact clinical and economic outcomes associated with Senza, however the impact of this is uncertain.

In summary:

- There is no new evidence to suggest that any earlier guidance should be updated.
- There is insufficient evidence to consider guidance development in any population sub-groups that did not previously receive a positive recommendation.
- As data submission to the UK Neuromodulation Registry was recommended in the MTG41 (2019), the EAG would strongly recommend that the results of the UK Neuromodulation Registry are considered in the context of this evidence review when published.

Appendix A – Relevant guidance

Appendix A1: NICE guidance – published

NICE guidelines (clinical, public health, social care, medicine practice guidelines, safe staffing)

Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. (2021) NICE guideline NG193

Low back pain and sciatica in over 16s (2016) NICE guideline NG59

Neuropathic pain in adults: pharmacological management in non-specialist settings. (2013) NICE guideline CG173

NICE quality standards

Low back pain and sciatica in over 16s (2017) quality standard QS155

NICE technology appraisals and highly specialised technologies

Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (2008) NICE technology appraisal guidance TA159

NICE interventional procedures, medical technologies or diagnostics guidance

Transcranial MRI-guided focused ultrasound thalamotomy for neuropathic pain (2018) NICE interventional procedures guidance IPG632

Transaxial interbody lumbosacral fusion for severe chronic low back pain (2018) NICE interventional procedures guidance IPG620

iFuse for treating chronic sacroiliac joint pain (2018) Medical technologies guidance MTG39

Minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain (2017) NICE interventional procedures guidance IPG578

Lateral interbody fusion in the lumbar spine for low back pain (2017) Interventional procedures guidance IPG574

Epiduroscopic lumbar discectomy through the sacral hiatus for sciatica (2016) interventional procedures guidance IPG570

Percutaneous transforaminal endoscopic lumbar discectomy for sciatica (2016) NICE interventional procedures guidance IPG556

Percutaneous interlaminar endoscopic lumbar discectomy for sciatica (2016) NICE interventional procedures guidance IPG555

Percutaneous intradiscal radiofrequency treatment of the intervertebral disc nucleus for low back pain (2016) NICE interventional procedures guidance IPG545

Percutaneous electrothermal treatment of the intervertebral disc annulus for low back pain and sciatica (2016) NICE interventional procedures guidance IPG544

Percutaneous coblation of the intervertebral disc for low back pain and sciatica (2016) NICE interventional procedures guidance IPG543

Insertion of an annular disc implant at lumbar discectomy (2014) NICE interventional procedures guidance IPG506

Peripheral nerve-field stimulation for chronic low back pain (2013) NICE interventional procedures guidance IPG451

Percutaneous electrical nerve stimulation for refractory neuropathic pain (2013) NICE interventional procedures guidance IPG450

Deep brain stimulation for refractory chronic pain syndromes (excluding headache) (2011) NICE interventional procedures guidance IPG382

Non-rigid stabilisation techniques for the treatment of low back pain (2010) NICE interventional procedures guidance IPG366

All other NICE guidance and advice products - MedTech, ESNM / Evidence Summary, ESUOM, Key Therapeutic Topic, QOF Indicator, and NICE CKS

Evoke Spinal Cord Stimulator for managing chronic neuropathic or ischaemic pain (2020) NICE medtech innovation briefing MIB238

Appendix A2: NICE guidance – in development

NICE guidelines

None identified

NICE quality standards

None identified

NICE technology appraisals and highly specialised technologies

None identified

NICE interventional procedures, medical technologies or diagnostics guidance

Neurostimulation of lumbar muscles for refractory non-specific chronic low back pain. NICE interventional procedures. Publication expected: September 2022

GID-MT567 Evoke Spinal Cord Stimulator for managing chronic neuropathic or ischaemic pain. NICE medical technologies. Publication expected: TBC

Percutaneous image-guided cryoablation of peripheral neuroma for chronic pain. NICE interventional procedures. Publication expected: TBC

All other NICE guidance and advice products - MedTech, ESNM / Evidence Summary, ESUOM, Key Therapeutic Topic, QOF Indicator, and NICE CKS

None identified

Appendix B – Literature search strategy

Appendix B1: Adverse Events Sources (results of NICE Information Services search)

FDA Medical Devices MAUDE database Premarket Notifications (510(k)s) Recalls of Medical Devices	
Search Date	**27/05/2022**

Premarket approvals:

FDA (2022) Senza Spinal Cord Stimulation (SCS) System – P130022/S042
- Approval order
- Premarket Approval (PMA)
- Summary of Safety and Effectiveness Data

FDA (2021) Senza Spinal Cord Stimulation System – P130022/S039
- Approval order
- Premarket Approval (PMA)
- Summary Of Safety And Effectiveness

FDA (2015) Nevro Senza Spinal Cord Stimulation (Scs) System – P130022 *(Original PMA)*
- Approval Order
- Summary Of Safety And Effectiveness

MAUDE database:
500 results were retrieved so these have been saved in a excel spreadsheet: Senza - FDA Maude Report 29 05 2022.xls (However, the EAG notes that the MAUDE database displays only 500 results, and on repeating the search, found over 900 results, as reported in section 4.7).

MHRA	
Search Date	**27/05/2022**
Nothing relevant found (However, the EAG repeated the search, and found one field safety notice, reported in section 4.7)	

Appendix B2: Trials (results of NICE Information Services search)

Search Date	**27/05/2022**

Ongoing studies

Comparison of HF10 Therapy Combined With CMM to CMM Alone in the Treatment of Non-Surgical Refractory Back Pain (NSRBP)
Trial identifier: NCT03680846
Status: Active, not recruiting
Indication: Back Pain
Devices: HF10 Therapy
Estimated completion date: November 2022
Country/ies: USA
Included by the EAG

Comparison of 10 kHz SCS Combined With CMM to CMM Alone in the Treatment of Neuropathic Limb Pain (SENZA-PDN)
Trial identifier: NCT03228420
Status: Active, not recruiting
Indication: Painful Diabetic Neuropathy
Devices: Senza HF10 Therapy
Estimated completion date: December 1, 2022
Country/ies: USA
Included by the EAG

Comparing Long-term Effectiveness of High Frequency and Burst Spinal Cord Stimulation
Trial identifier: NCT03681262
Status: Recruiting
Indication: Chronic Pain
Devices: High frequency spinal cord stimulation
Estimated completion date: December 31, 2026
Country/ies: USA
Included by the EAG

Completed studies

Clinical Trial of the Senza™ SCS System in the Treatment of Chronic Upper Limb and Neck Pain (SENZA-ULN)
Trial identifier: NCT02385201
Status: Completed
Indication: Neck pain / Chronic Pain
Devices: Senza
Completion date: March 2018
Country/ies: USA
Publication: N/A
Excluded by the EAG: Upper limb and neck

SCS for the Treatment Of Chronic Pain of the Upper Extremities (UEP)
Trial identifier: NCT02703818
Status: Completed
Indication: Upper Extremity Pain
Devices: Senza
Completion date: May 2018
Country/ies: USA
Publication:
Burgher A, Kosek P, Surrett S, Rosen SM, Bromberg T, Gulve A, Kansal A, Wu P, McRoberts WP, Udeshi A, Esposito M, Gliner BE, Maneshi M, Rotte A, Subbaroyan J. Ten kilohertz SCS for Treatment of Chronic Upper Extremity Pain (UEP): Results from Prospective Observational Study. J Pain Res. 2020 Nov 10;13:2837-2851. doi: 10.2147/JPR.S278661. eCollection 2020.
Excluded by the EAG: Upper extremities

A Feasibility Clinical Trial to Evaluate High Frequency Spinal Cord Stimulation for the Treatment of Patients With Chronic Migraine (rCM HF-SCS)
Trial identifier: NCT01653340
Status: Completed
Indication: Refractory Chronic Migraine
Devices: Senza
Completion date: February 2014
Country/ies: Italy
Publication: N/A
Excluded by the EAG: Migraine

Unknown Status / terminated studies
Sham-Controlled RCT on 10kHz High-Frequency Spinal Cord Stimulation for Chronic Neuropathic Low Back Pain (Modulate-LBP) (Modulate-LBP)
Trial identifier: NCT03470766
Status: Unknown
Indication: Chronic low back pain / Neuropathic Pain / Refractory Pain
Devices: Senza
Estimated completion date: August 1, 2020
Country/ies: Guy's and St Thomas, UK
Included by the EAG

A Prospective, Open Label, Pilot Study of Patient OutcoMes Following Successful TriAl of High Frequency SpInal CorD Stimulation at 10kHz (HF10™) Leading to Permanent Implant Compared to Trial Failure and Standard CarE for the TreatmeNt of Persistent Low BACK Pain of Neuropathic Origin (Maiden Back)
Trial identifier: NCT02689375
Status: Unknown
Indication: Palliative Care
Devices: Senza
Estimated completion date: October 31, 2021
Country/ies: Leeds, UK
Included by the EAG

Comparison of Senza to Commercial Spinal Cord Stimulation for the Treatment of Chronic Pain (SENZA-RCT)
Trial identifier: NCT01609972
Status: Unknown
Indication: Chronic Low Back Pain
Devices: Spinal Cord Stimulator

Completion date: June 2015 Country/ies: USA Publication: Amirdelfan K, Yu C, Doust MW, Gliner BE, Morgan DM, Kapural L, Vallejo R, Sitzman BT, Yearwood TL, Bundschu R, Yang T, Benyamin R, Burgher AH, Brooks ES, Powell AA, Subbaroyan J. Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT. Qual Life Res. 2018 Aug;27(8):2035-2044. doi: 10.1007/s11136-018-1890-8. Epub 2018 Jun 1. **Paper included by the EAG**

Appendix B3: Database searches

Databases*	Date searched	No retrieved	Version/files
MEDLINE (Ovid)	28/05/2022	224	1946 to May 27, 2022
MEDLINE In-Process (Ovid)	28/05/2022	0	1946 to May 27, 2022
Medline ePub ahead of print (OVID)	28/05/2022	20	May 27, 2022
EMBASE (Ovid)	28/05/2022	270	1996 to 2022 May 27
Embase Conference (OVID)	28/05/2022	463	1996 to 2022 May 27
CDSR (Wiley)	28/05/2022	0	Issue 5 of 12, May 2022
CENTRAL (Wiley)	28/05/2022	55	Issue 4 of 12, April 2022
CENTRAL conferences	28/05/2022	84	Issue 4 of 12, April 2022
**Database of Abstracts of Reviews of Effects – DARE (CRD)	28/05/2022	0	n/a
HTA database (CRD)	28/05/2022	0	n/a
HTA database (INAHTA)	28/05/2022	7	n/a
Epistemonikos	28/05/2022	28	n/a
Total		***1151***	
Total after deduplication		**767**	

*****From January 2015 no new records/commentaries will be added to DARE or NHS EED.***

Database strategies: Ovid MEDLINE(R) <1946 to May 27, 2022>
1 (Senza* or Nevro*).af.25185 2 MTG41.af. 0 3 (NCT02385201 or NCT01609972 or NCT02703818 or NCT03228420 or NCT01653340 or NCT02689375 or NCT03470766 or NCT03680846 or NCT03681262).af. 8 4 or/2-3 8 5 Spinal Cord Stimulation/ 1555

6 ((spinal* or spine* or column* or epidur* or back) adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 16031
7 (SC adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 2531
8 SCS.tw. 8432
9 or/5-8 25511
10 (Highfrequen* or High-frequen*).tw. 83983
11 ("HF10" or "HF-10" or 10 khz or 10khz or 10kilohert* or 10-kilohert* or 10kilo-hert* or 10-kilo-hert* or 10,000hz or 10,000-hz or 10000hz or 10000-hz or 10,000hert* or 10,000-hert* or 10000hert* or 10000-hert*).tw. 1973
12 (HFSCS or HF-SCS).tw. 199
13 or/10-12 85739
14 9 and 13 398
15 1 and 9 93
16 4 or 14 or 15 445
17 Animals/ not Humans/4977294
18 16 not 17 318
19 limit 16 to english language 397
20 limit 19 to ed=20170601-20220528 224

Database strategies: Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to May 27, 2022>

1 (Senza* or Nevro*).af.0
2 MTG41.af. 0
3 (NCT02385201 or NCT01609972 or NCT02703818 or NCT03228420 or NCT01653340 or NCT02689375 or NCT03470766 or NCT03680846 or NCT03681262).af. 0
4 or/2-3 0
5 Spinal Cord Stimulation/ 0
6 ((spinal* or spine* or column* or epidur* or back) adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 2
7 (SC adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 0
8 SCS.tw. 2
9 or/5-8 4
10 (Highfrequen* or High-frequen*).tw. 24
11 ("HF10" or "HF-10" or 10 khz or 10khz or 10kilohert* or 10-kilohert* or 10kilo-hert* or 10-kilo-hert* or 10,000hz or 10,000-hz or 10000hz or 10000-hz or 10,000hert* or 10,000-hert* or 10000hert* or 10000-hert*).tw. 1
12 (HFSCS or HF-SCS).tw. 0
13 or/10-12 25
14 9 and 13 0
15 1 and 9 0
16 4 or 14 or 15 0

Database strategies: Ovid MEDLINE(R) Epub Ahead of Print <May 27, 2022>

1 (Senza* or Nevro*).af.25

2 MTG41.af. 0
3 (NCT02385201 or NCT01609972 or NCT02703818 or NCT03228420 or NCT01653340 or NCT02689375 or NCT03470766 or NCT03680846 or NCT03681262).af. 0
4 or/2-3 0
5 Spinal Cord Stimulation/ 0
6 ((spinal* or spine* or column* or epidur* or back) adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 351
7 (SC adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 29
8 SCS.tw. 256
9 or/5-8 564
10 (Highfrequen* or High-frequen*).tw. 1000
11 ("HF10" or "HF-10" or 10 khz or 10khz or 10kilohert* or 10-kilohert* or 10kilo-hert* or 10-kilo-hert* or 10,000hz or 10,000-hz or 10000hz or 10000-hz or 10,000hert* or 10,000-hert* or 10000hert* or 10000-hert*).tw. 34
12 (HFSCS or HF-SCS).tw. 9
13 or/10-12 1032
14 9 and 13 17
15 1 and 9 3
16 4 or 14 or 15 20

Database strategies: Embase <1996 to 2022 May 27>

1 (Senza* or Nevro*).af.5613
2 MTG41.af. 0
3 (NCT02385201 or NCT01609972 or NCT02703818 or NCT03228420 or NCT01653340 or NCT02689375 or NCT03470766 or NCT03680846 or NCT03681262).af. 37
4 or/2-3 37
5 *spinal cord stimulation/ 4727
6 ((spinal* or spine* or column* or epidur* or back) adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 24442
7 (SC adj2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)).tw. 3915
8 SCS.tw. 15695
9 or/5-8 39737
10 (Highfrequen* or High-frequen*).tw. 104785
11 ("HF10" or "HF-10" or 10 khz or 10khz or 10kilohert* or 10-kilohert* or 10kilo-hert* or 10-kilo-hert* or 10,000hz or 10,000-hz or 10000hz or 10000-hz or 10,000hert* or 10,000-hert* or 10000hert* or 10000-hert*).tw. 3078
12 (HFSCS or HF-SCS).tw. 487
13 or/10-12 107340
14 9 and 13 1198
15 1 and 9 370
16 4 or 14 or 15 1267
17 Nonhuman/ not Human/ 3764030
18 16 not 17 1102
19 limit 18 to english language 1068
20 limit 19 to dc=20170601-20220528 733

21	limit 20 to (conference abstract or conference paper or "conference review")	463
22	20 not 21	270

Database strategies: CDSR, CENTRAL and CENTRAL Conferences

#1	(Senza* or Nevro*)	873
#2	MTG41	0
#3	(NCT02385201 or NCT01609972 or NCT02703818 or NCT03228420 or NCT01653340 or NCT02689375 or NCT03470766 or NCT03680846 or NCT03681262)	19
#4	{or #2-#3}	19
#5	MeSH descriptor: [Spinal Cord Stimulation] explode all trees	92
#6	((spinal* or spine* or column* or epidur* or back) near/2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)):ti,ab,kw	5946
#7	(SC near/2 (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)):ti,ab,kw	1768
#8	SCS:ti,ab,kw	1083
#9	{or #5-#8}	8222
#10	(Highfrequen* or High-frequen*):ti,ab,kw	6567
#11	("HF10" or "HF-10" or "10 khz" or "10khz" or "10kilohert*" or "10-kilohert*" or "10kilo-hert*" or "10-kilo-hert*" or "10,000hz" or "10,000-hz" or "10000hz" or "10000-hz" or "10,000hert*" or "10,000-hert*" or "10000hert*" or "10000-hert*"):ti,ab,kw	120
#12	(HFSCS or HF-SCS):ti,ab,kw	44
#13	{or #10-#12}	6639
#14	#9 and #13	220
#15	#1 and #9	77
#16	#4 or #14 or #15 with Publication Year from 2017 to 2022, with Cochrane Library publication date Between Jun 2017 and May 2022, in Trials	164
#17	(clinicaltrials or trialsearch):so	398994
#18	#16 not #17	139
#19	"conference":pt	198434
#20	#18 and #19	84
#21	#18 not #19	55

Database strategies: DARE and HTA

Line	Search	Hits
1	(Senza* or Nevro*)	0
2	(MTG41)	0
3	(NCT02385201 or NCT01609972 or NCT02703818 or NCT03228420 or NCT01653340 or NCT02689375 or NCT03470766 or NCT03680846 or NCT03681262)	0
4	#1 OR #2 OR #3	0
5	MeSH DESCRIPTOR Spinal Cord Stimulation EXPLODE ALL TREES	9
6	(((spinal* or spine* or column* or epidur* or back) near (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)))	890

7 ((SC near (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*))) 17
8 (SCS) 40
9 #5 OR #6 OR #7 OR #8 926
10 ((Highfrequen* or High-frequen*)) 136
11 (("HF10" or "HF-10" or "10 khz" or "10khz" or "10kilohert*" or "10-kilohert*" or "10kilo-hert*" or "10-kilo-hert*" or "10,000hz" or "10,000-hz" or "10000hz" or "10000-hz" or "10,000hert*" or "10,000-hert*" or "10000hert*" or "10000-hert*")) 0
12 ((HFSCS or HF-SCS)) 0
13 #10 OR #11 OR #12 136
14 #9 AND #13 3
15 #4 OR #14 3
16 * FROM 2017 TO 2022 506
17 #15 AND #16 0

Database strategies: INAHTA

17 #16 AND #15 7
16 * FROM 2017 TO 2022 2258
15 #14 OR #4 38
14 #13 AND #9 38
13 #12 OR #11 OR #10 3136
12 (HFSCS or HF-SCS) 15
11 ("HF10" or "HF-10" or "10 khz" or "10khz" or "10kilohert*" or "10-kilohert*" or "10kilo-hert*" or "10-kilo-hert*" or "10,000hz" or "10,000-hz" or "10000hz" or "10000-hz" or "10,000hert*" or "10,000-hert*" or "10000hert*" or "10000-hert*") 4
10 Highfrequen* or High-frequen* 3127
9 #8 OR #7 OR #6 OR #5 94
8 SCS 15
7 SC near (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*) 76
6 (spinal* or spine* or column* or epidur* or back) NEAR (stimulat* or therap* or treat* or electrostimulat* or electro-stimulat*)10
5 "Spinal Cord Stimulation"[mh] 8
4 #3 OR #2 OR #1 1
3 NCT02385201 or NCT01609972 or NCT02703818 or NCT03228420 or NCT01653340 or NCT02689375 or NCT03470766 or NCT03680846 or NCT036812620
2 MTG41 0
1 Senza* or Nevro* 1

Database strategies: Epistemonikos

(title:(Senza* OR Nervo*) OR abstract:(Senza* OR Nervo*)) AND (title:(Spinal Cord Stimulation) OR abstract:(Spinal Cord Stimulation))

Publication year limited to the last 5 years.

Conferences

Search Date	**27/05/2022**
Conferences were identified during searches in Embase and CENTRAL. Search numbers are shown in the table above and the results are included in the Eppi review. These can be filtered in or out when sifting in Eppi using the sources option in the filters.	

Search Notes:

Database searches were limited from June 2017. No date limits were applied to the others sources.

Appendix C – Details of excluded studies

#	Source	Study reference	Reason for exclusion
1.	Updated NICE literature search	Ahmadi *et al.* (Neuromodulation. 2017; 348-353)	Study size: n<10
2.	Updated NICE literature search	Al-Kaisy et al. (Pain Med. 2018; 1219-1226)	Considered during original guidance development at consultation
3.	Updated NICE literature search	Al-Kaisy *et al.* (Scientific Reports. 2019; 9: 11441)	No additional follow up or outcomes reported beyond those included for the same study in the original Assessment Report.
4.	Updated NICE literature search	Al-Kaisy *et al.* (Anaesthesia. 2020; 775-784)	No additional follow up or outcomes reported beyond those included for the same study in the original Assessment Report.
5.	Updated NICE literature search	Al-Kaisy (Reg Anesth Pain Med. 2020b; 883-890)	Population: Mixed population (results not reported separately) Intervention: Mixed interventions (results not reported separately) Device not reported
6.	Company search	Al-Kaisy *et al.* (Trials. 2020c; 111); NCT03470766	Study design: Modulate-LBP trial design
7.	Updated NICE literature search	Amirdelfan *et al.* (Quality of Life Res. 2018; 2035-2044)	No additional follow up or outcomes reported beyond those included for the same study in the original Assessment Report.
8.	Company search	Amirdelfan *et al.* (J Pain Res. 2021; 2991-2999)	Intervention: not HF-10 SCS (HFIT, 30-150kHz, competitor)
9.	Updated NICE literature search	Andrade (Neuromodulation, 2021; 540-545)	Population: Mixed population (results not reported separately) Intervention: Mixed interventions (results not reported separately)
10.	Updated NICE literature search	Baranidharan (Neuromodulation. 2021; 479-487)	Intervention: Device not reported
11.	Company search	Benyamin *et al.* (Pain Physician. 2020; 87-98)	Intervention: not HF-10 SCS (HD-SCS, Medtronic devices)
12.	Updated NICE literature search	Billet (Pain Manag. 2022; 75-85)	Mixed population (results not reported separately)
13.	Company search	Billot *et al.* (Trials. 2020; 696); NCT03014583	Study design: MULTIWAVE study completed as of Nov 2021, no results published
14.	Company search	Bolash *et al.* (Pain Med. 2019; 1971-1979)	Intervention: not Senza device (StimWave Freedom SCS)
15.	Company search	Bolash *et al.* (Pain Physician. 2022; 67-76)	Intervention: Not Senza device (Freedom-8 SCS), not high frequency spinal cord stimulation (10 Hz - 1500Hz)
16.	Updated NICE literature search	De Andres et al. (Pain Med. 2017; 2401-2421)	Considered during original guidance development at consultation

#	Source	Study reference	Reason for exclusion
17.	Updated NICE literature search	De Carolis (Pain Physician. 2017; 331-341)	Outcome: Outcome out of scope
18.	Company search	De Groote *et al.* (Neuroimage Clin. 2019; 102087)	Intervention: not HF-10 SCS (HD-SCS, RestoreSensor, Medtronic)
19.	Company search	De Jaeger *et al.* (J Clin Med. 2020;3126); NCT02787265	Intervention: not HF-10 SCS (HD-SCS, Medtronic devices)
20.	Company search	De Jaeger *et al.* (Neuromodulation. 2020; 546-555); NCT02787265	Intervention: not HF-10 SCS (HD-SCS; Restore or PrimeAdvanced IPG Medtronic)
21.	Updated NICE literature search	Do (Pain Pract. 2021; 215-225)	Population: Mixed population (results not reported separately)
22.	Updated NICE literature search	Feng (J Pain Res. 2021; 2593-2600)	Population: Mixed population (results not reported separately)
23.	Updated NICE literature search; Company search	Galan (Pain Management, 2020; 291-300)	Study size: n<10
24.	Updated NICE literature search	Galan (Pain Pract. 2021; 898-906)	Population: Mixed population (results not reported separately)
25.	Updated NICE literature search	Ghosh (Pain Pract. 2020; 706-713)	Population: Mixed population (results not reported separately)
26.	Updated NICE literature search	Gill (Pain Pract. 2019; 289-294)	Population: Mixed population (results not reported separately)
27.	Company search	Goudman *et al.* (Neuromodulation. 2019; 74-81); NCT02751216	Intervention: not HF-10 SCS (HD-SCS, RestoreSensor, Medtronic)
28.	Company search	Goudman *et al.* (J Clin Med. 2020; 4131); NCT04500691	Intervention: Not specific to Senza (Nevro and Medtronic listed in acknowledgements; no additional detail on clinicaltrials.gov)
29.	Updated NICE literature search; Company search	Goudman (J Neurosurg Spine. 2020; 440-448)	Intervention: Not HF-10 SCS (RestoreSensor, Intellis or PrimeAdvanced internal pulse generator by Medtronic)
30.	Company search	Goudman *et al.* (Neuromodulation. 2021; 520-531); NCT02787265	Intervention: not Senza (RestoreSensor, Intellis or PrimeAdvanced internal pulse generator by Medtronic)
31.	Company search	Goudman et al. (Pain. 2021; 582-590); NCT02787265	Intervention: not HF-10 SCS (HD-SCS; RestoreSensor, Intellis, or PrimeAdvanced EPG by Medtronic)
32.	Updated NICE literature search	Gupta (Pain Pract. 2020; 908-918)	Population: Mixed population (results not reported separately)
33.	Updated NICE literature search	Gupta et al. (Pain Res Manag. 2021; 6639801)	Population: Mixed population (results not reported separately)
34.	Updated NICE literature search	Gupta *et al.* (Journal of Pain Research. 2021; 3675-3683)	Population: Mixed population (results not reported separately)

#	Source	Study reference	Reason for exclusion
35.	Updated NICE literature search	Hagedorn (Neuromodulation. 2021; 499-506)	Population: Mixed population (results not reported separately)
36.	Updated NICE literature search	Hagedorn (Neuromodulation. 2021; e13497)	Population: Mixed population (results not reported separately)
37.	Company search	Hamm-Faber *et al.* (Neuromodulation. 2020; 118-125)	Intervention: Not HF10 (not senza)
38.	Updated NICE literature search	Kapural (J Pain Res. 2020; 2861-2867)	Population: Mixed population (results not reported separately) Intervention: Device not reported
39.	Updated NICE literature search	Kapural (Neurosurgery. 2016; 667-677)	Included in original Assessment Report
40.	Company search	Maatta *et al.* (Pain Physician. 2019; E37-E44)	Intervention: Not specific to Senza (devices not specified)
41.	Company search	Morales *et al.* (Curr Pain Headache Rep. 2019; 25)	Study design: review: - Kapural *et al.* 2015 Senza RCT (Included in original Assessment Report - Kapural *et al.* 2016 (Included in original Assessment Report) - Deer *et al.* 2018: SUNBURST trial (Intervention: Prodigy, Abbot):
42.	Updated NICE literature search; Company search	Motov et al. (Neurosurgical Review. 2021; 2809-2818)	Population: Mixed population (results not reported separately)
43.	Company search	Nissen *et al.* (Neuromodulation. 2020; 102-111)	Intervention: not HF-10 SCS (SCS using Resume, Symmix, Specify devices by Medtronic)
44.	Company search	O'Connell *et al.* (Cochrane Database Syst Rev. 2021; CD013756)	Study design: SR - Al-Kaisy *et al.* 2018b (Intervention: Medtronic) - Kriek *et al.* 2017 (Intervention: St Jude Medical, Eon device) - Perruchoud *et al.* 2013 (Intervention: Medtronic RestoreADVANCED, RestoreSensor, RestoreUltra, PrimeADVANCED devices) - Sokal *et al.* 2020 (Intervention: Boston Scientific Precision Novi, Montage devices)
45.	Updated NICE literature search	Ontario Health (Quality) (Ont Health Technol Assess Ser. 2020; 1-109)	Study design
46.	Updated NICE literature search	Parikh (Pain Medicine Case Reports. 2021; 37-44)	Population: Mixed population (results not reported separately)
47.	Updated NICE literature search; Company search	Patel (Pain Pract. 2021; 171-183)	Study design

#	Source	Study reference	Reason for exclusion
48.	Company search	Peeters *et al.* (World Neurosurg. 2020; e331-e340)	Study Design: Literature review snowballed: - Van Buyten *et al.* 2013 (Included in original Assessment Report) - Al-Kaisy *et al.* 2014 (Included in original Assessment Report)
49.	Updated NICE literature search	Salmon *et al.* (Postgraduate Medicine. 2019; 230-238)	Population: Mixed population (results not reported separately)
50.	Updated NICE literature search; Company search	Sclafani (PM R. 2019; 1346-1353)	Study design: Feature counterpoint (expert discussion)
51.	Updated NICE literature search	Sills (Postgrad Med. 2020; 352-357)	Study design
52.	Company search	Simopoulos *et al.* (Pain Pract. 2019; 794-799)	Intervention: not HF-10 SCS (all underwent epidural placement of low-frequency SCS devices)
53.	Updated NICE literature search	Sokal (J Clin Med. 2020; 2810)	Intervention: Device out of scope
54.	Updated NICE literature search	Strand (J Diabetes Sci Technol. 2022; 332-340)	Study design
55.	Updated NICE literature search	Surges (Pain Ther. 2021; 1255-1268)	Population: Mixed population (results not reported separately)
56.	Updated NICE literature search	Sweeney (Clin Neurol Neurosurg. 2022; 216)	Population: Mixed population (results not reported separately) Device not reported
57.	Updated NICE literature search	Wang (Neuromodulation. 2021; 507-511)	Population: Mixed population (results not reported separately)
58.	Updated NICE literature search	Wood (Nat Rev Neurol. 2021; 262)	Study design

Appendix D – Study characteristics of included clinical evidence (N=10 studies)

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
1.	Peterson *et al.* (2021) Peterson *et al.* (2022a) Peterson *et al.* (2022b) US NCT03228420	Design: Cross-over RCT (n=216) 1:1 block randomisation by site, stratified by glycaemic control and pain severity, treated as single arm study, Patients offered crossover if <5cm on VAS scale at 6 months Intervention: High-frequency, Senza 10 kHz (Nevro), plus CMM (n=113; 90 successfully implanted following device trial) ☑☒ Comparator: CMM ☒	Included: adults 22 years and older with painful diabetic neuropathy symptoms for at least 12 months, refractory to medications, previously taking pregabalin or gapapentin plus 1 other class of analgesic, current stable dosage of analgesic medications for at least 30 days, lower limb pain at least 5 cm on 10 cm VAS, and medically suitable for proposed procedure ☑ Excluded: HbA_{1C} >10%, BMI >45 kg/m^2, daily opioid dose greater than 120 MME, upper limb pain intensity at least 3 cm on VAS, have a diagnosis of progressive neurological disorder, a diagnosis of coagulation disorder, prior experience with SCS or other nerve stimulation therapies for chronic pain, additional pain treatment for lower limb pain up to 30 days prior, existing drug pump, condition indicating need for MRI or Diathermy treatment, metastatic malignancy and life expectancy of less than one year. ☑☒ Recruitment: 28 August 2017 – 23 August 2019 Setting: Multi-centre; academic and community pain clinics (n=18)	Primary: lower limb pain relief on VAS with >50% or VAS score 3cm with additional pain assessment via SF-MPQ-2 subscales, DN4 and modified Neuropathy symptom score with responder rate (at least 50% pain relief from baseline), pain responders of crossover. EQ-5D-5L HQoL, patient satisfaction score, adverse event monitoring and related neurological deficit monitoring. Neurological functional test 10-point diabetic foot assessment, semmes-Weinstein 10g filament testing. ☑☒ Secondary: trial success, measurement of lower limb pain relief <3cm VAS, crossover of subjects, lower limb pain	Comparator of CMM out of scope, so treated as a single arm study. Only patients with upper limb pain intensity of at least 3 cm on VAS were explicitly excluded, suggesting inclusion of some patients who had upper limb pain below the threshold. Stated lead placement in region T8-T11 region.

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
				relief >5cm VAS, readmissions, improvement of neurological and health related quality of life, percentage change in HbA1c. Outcomes measured at baseline, 1, 3, 6, 9 and 12 months	
2.	Kapural *et al.* (2022) US NCT03680846 [Trial protocol: Patel *et al.* 2021]	Design: Cross-over RCT, n=159 (randomised 1:1 using permuted block sizes per site). Patients able to cross over at 6 months if <50% pain relief observed Intervention (n=82 High-frequency, Senza 10 kHz (Nevro) plus CMM. Trial up to 14 days, only subjects reporting greater than 50% reduction in pain were then subsequently implanted with permanent implant ☑ ☑☒ Comparator (n=76, of which 67 wanted to cross-over at 6 months): CMM ☒	Included: CMM had failed, diagnosis of chronic, axial, low back pain with a neuropathic component, and no previous spine surgery, deemed as inappropriate candidates for spine surgery (by a spine surgeon). Additional inclusion criteria listed in Patel et al. 2021: have not had any surgery for back or leg pain, or any surgery resulting in back or leg pain, average back pain intensity of at least 5 cm out of 10 cm on VAS, stable pain medication for at least 28 days prior to enrolment, adults 18 years or older, able to give informed consent, willing and able to comply with study-related requirements, procedures and visits, be capable of subjective evaluation (read and understand written questionnaires in local language) ☑ Exclusions (from Patel *et al.* 2020): patients with diagnosed back condition with inflammatory causes of back pain, conditions	Primary: responder rate, of at least 50% pain relief on VAS ☑ Secondary: trial success, proportion of patients with at least 10 point decrease in ODI from baseline, percentage change from baseline in back pain on VAS, proportion of patients reporting “better” or “a great deal better” on PGIC, mean change from baseline in EQ-5D-5L, mean change in opioid use, adverse events and neurological assessment ☑	Comparator of CMM out of scope, so treated as a single arm study. Authors acknowledge inability to blind arms, CMM varying across sites, as limitations of their study. The study was funded by Nevro.

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
			or pain in other areas that could interfere with study procedures, accurate pain reporting or otherwise confound evaluation of study endpoints, evidence of active disruptive psychological or psychiatric disorder, or other condition significant enough to impact pain perception, intervention compliance, or evaluation of treatment outcome, current diagnosis of progressive neurological disease, spinal cord tumour, or critical spinal stenosis, current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease, or uncontrolled diabetes mellitus, interventional procedure within 30 days prior to enrolment to treat back or leg pain, opioid addiction or drug-seeking behaviour, existing drug pump or SCS system or another active implant device such as pacemaker, prior experience with neuromodulation devices, have condition currently requiring or likely require use of diathermy or MRI, metastatic malignant disease or active local malignant disease, life expectancy less than 1 year, active systemic or local infection, pregnant, significant untreated additional to dependency-producing medications or substance abuser within 6 months of enrolment, be concomitantly participating in another clinical study, involved in injury claim under current litigation, have a pending or approved worker's compensation claim. ☑	Outcomes measured at 1, 3, 6, 9 and 12 months.	

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
			Recruitment: 5 September 2018 to 27 January 2020 Setting: multi-centre (N=15 from Patel *et al.* 2021)		
3.	Kallewaard *et al.* (2021) Netherlands	Design: Prospective cohort – single arm (n=68, 58 with successful implantation) Intervention High-frequency, Senza 10 kHz (Nevro). Trial of 10 kHz SCS with duration of 7 to 21 days. Only subjects reporting greater than 50% reduction in lower leg pain were then subsequently implanted with permanent implant. implanted within 14 days☑ Comparator: N/A	Included: adults 18 years or older with FBSS refractory to conservative therapy and minimally invasive pain procedures for at least 3 months, with average leg pain intensity at least 5 cm on VAS, average back pain intensity no greater than average leg pain intensity, had stable medication regime for 4 weeks before baseline visit, could use study equipment, and comply with study requirements ☑ Excluded: patients with pain in 1 or more areas not intended for SCS treatment, mechanical spinal instability requiring fusion, pain significantly exacerbated by activity or alleviated by rest, non-neuropathic pain, leg or back pain improvement in 30 days prior to enrolment as a result of interventional procedure or surgery, prior experience with SCS, active psychological or psychiatric disorder significant enough to impact pain perception, intervention compliance, or ability to evaluate treatment outcome, coagulation disorders, and pregnancy ☑ Recruitment: April 2015 to September 2017 Setting: Multi-centre (n=5)	Primary: responder rate at 12 months, defined as at least 50% improvement in leg pain on VAS ☑ Secondary: trial success, responder rate prior to 12 months; proportion reporting at least 50% improvement in baseline back pain on VAS, changes in baseline pain intensity on VAS; ODI, GIC, PCS, HAD, medication use and change in opioid dose ☑ Outcomes reported at baseline, 1, 3, 6 and 12 months	Author stated that five patients suffered serious adverse events but that these were resolved, no additional details given. Lead author is a consultant for Nevro Corp. Several employees of Nevro Corp were also authors.

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
4.	Cordero Tous *et al.* (2021) Spain	Design: Prospective Cohort – single arm (n=18) Intervention: High-frequency, Senza 10 kHz (Nevro) for rescue therapy after failed low frequency SCS. Trial period (up to 2 weeks) with up to three different trial programs used. Only subjects reporting greater than 50% improvement in condition were then subsequently implanted with permanent implant ☑ Comparator: N/A	Included: patients suffering from CRPS or FBSS in whom pharmacological and invasive treatments (for example, nerve blocks and neuroaxial blocks) have failed, and who had mental health assessment before implantation of low frequency SCS device, and had an unsuccessful trial or loss of efficacy during follow up and had discontinued low frequency SCS ☑ Excluded: patients whose low frequency SCS device leads were outdated and could not be connected to the high frequency device ☑ Recruitment: October 2016 to October 2018 Setting: Single centre; hospital-based referral for neuromodulation therapy	Primary: Lumbar region pain intensity using VAS, Limb pain intensity using VAS, QoL measured by FRI, analgesic use PGI-I ☑ Secondary: Trial success, BMI effect on pain relief following permanent implantation Outcomes measured at baseline and end of trial period; 12 months after permanent implantation.	All patients had tried and discontinued low-frequency SCS. Refers to “limbs” being affected but does not state whether they are upper or lower.
5.	De Groote *et al.* (2020) Belgium NCT02650362	Design: Prospective cohort – single arm (n=11) Intervention: High-frequency, Senza 10 kHz (Nevro). Trial period of four weeks only subjects reporting greater than 50% reduction in pain and	Included: patients with FBSS, chronic intractable pain of the trunk or limbs that remained refractory to conservative therapy, stable neurological function for previous 30 days ☑ Excluded: patients with extreme fear of MRI, general MRI contraindications, or life expectancy less than 6 months, an active	Primary: Measurement of volumetric structural brain alterations using voxel based morphometry, MRI on regions of interest for volumetric alterations ☒	Brain imaging component of study out of scope, but pain outcomes reported independently. Study supported by independent research

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
		reduction of >50% of analgesic medication, were then subsequently implanted with permanent implant ☑☑ Comparator: N/A	infection at time of study, coagulation disorder, malignancy diagnosed within last 2 years. ☑ Recruitment: January 2016 to July 2017 Setting: Single centre, University Hospital	Secondary: Back and leg pain intensity reported separately on NRS (3 times daily for 2 weeks before MRI visit), PCS, sleep quality measured by actigraphy and PSQI ☑ Outcomes measured at baseline, 1 and 3 months	grants from Nevro Corp.
6.	Chen *et al.* (2022) US	Design: Retrospective cohort – single arm (n=89) Intervention: High-frequency, Senza 10 kHz (Nevro). Temporary trial of 10 kHz stimulation, duration not reported; site best practice. Only subjects reporting greater than 50% reduction of pain relief were then subsequently implanted with permanent implant ☑ Comparator: N/A	Included: Adults 18 years or older with painful diabetic peripheral neuropathy. Consent for their data to be used. ☑ Excluded: not reported Recruitment: May 2017 to November 2020 Setting: Multi-centre; commercial data (number of centres not reported)	Primary: Percentage of pain relief (0%-100%) defined as 50% a successful response ☑ Secondary: Improvement in sleep, improvement in overall function, device inactivation ☑ Measured at baseline, 3, 6, 12 and 24 months after permanent implantation	Follow up intervals varied according to each centre's standard protocol and thus were not uniformed time points. Primary pain locations described at baseline in table and further stated pain etiology is pDPN and bilateral foot pain but is presented only as reduction of pain. Commercial registry data (HFXCloudTM) used to retrieve anonymised data

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
					Author reports possibility of selection bias due to nature of insurance approval and lack of randomization in study population. Figure 1 suggests possible inclusion of patients with neuropathy affecting the hands, although this is not reported explicitly, and not a primary pain location (Table 1).
7.	Torres-Bayona *et al.* (2021) Colombia	Design: Retrospective cohort (n=62) Intervention High-frequency, Senza 10 kHz (Nevro). All patients underwent 7 to 10 trial only subjects reporting greater than 50% reduction in pain were then subsequently implanted with permanent implant ☑ Comparator: N/A	Included: adults 18 years or older with variable pathologies (including FBSS and NeppLL), with permanent implant and follow up at least 6 months, with prior successful trial before permanent implantation ☑ Excluded: not reported Recruitment: January 2016 to August 2018 Setting: Single centre	Primary: VAS measurement of pain relief obtained, successful responders deemed to be at least 50% pain reduction with no stimulation-related neurological deficit ☑☒ Secondary: trial success, pain distribution, complications, degree of pain relief, pain scores on VAS (at baseline, trial, and after implantation) ☑☒	Stated lead placement in region T8-T11 region.

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
				Pain outcomes compared to baseline at conclusion of study follow up. Measured at baseline, trial and postoperative pain. Mean follow up time of 11 months.	
8.	DiBenedetto *et al.* (2018) US	Design: Retrospective propensity matched cohort, 2:1 ratio (n=96) Intervention (n=32): High-frequency, Senza 10 kHz (Nevro), plus CMM. Active patients at pain centre for at least 12 months before and after implantation, and did not have explant of device during study period. Trial period of 7 to 10 days. Only patients with a minimum 50% reduction in pain and marked improvement in function (undefined) proceeded to permanent implantation ☑☒ Comparator (n=64): CMM ☒	Included: patients with chronic low back pain, with or without radicular lower extremity pain. Evaluation by interventional anaesthesiologist and pain psychologist, however within retrospective study, measures were developed over time and not all measures were administered to all patients at their 10 kHz evaluation. ☑☒ Excluded: not reported Recruitment: 01 December 2014 to 31 December 2017 Setting: Single-centre, community based interdisciplinary pain management centre	Pain (FPS, NRS), disability (RMDQ-m, WHODAS 2.0), opioid dose, healthcare utilisation (office visits and procedures). ☑ Outcomes reported at baseline and 12 months follow-up.	Comparator of CMM out of scope, so treated as a single arm retrospective cohort study (n=32). Authors acknowledge retrospective design, subjective measures of disability, small sample size and only 12 month follow-up as limitations of their study.

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
9.	Abraham *et al.* (2021) US	Design: Retrospective cohort – single arm (n=21) Intervention: High-frequency, Senza Omnia 10 kHz (Nevro) Trial up to five to seven days only subjects reporting greater than 50% reduction in pain were then subsequently implanted with permanent implant ☑☑ Comparator: N/A	Included: all patients with chronic pain syndrome, including FBSS and sciatica, with at least 12 months of prior medical management, all patients underwent multi-disciplinary medical evaluation ☑ Excluded: not reported Recruitment: February 2018 to February 2019 Setting: Single centre	Primary: Pain relief on VAS scale with no responder success condition, use of pain medication, activities of daily living, quality of sleep ☑ Outcomes measured at baseline, 3, 6, 9 and 12 months	Study identified by company only but authors declared no recipe of funding or resources from any organisation with interest. If VAS pain score between lower back and lower limb pain the mean of the score was presented. Authors acknowledge limited robustness of study using chart based retrospective data and small population size.
10.	Sayed *et al.* (2020) US	Design: Retrospective Cohort – single arm (n=19) Intervention: High-frequency, Senza 10 kHz (Nevro). All patients underwent a 5 to 10 day trial only subjects reporting greater than 50% improvement in pain relief were then subsequently implanted with permanent implant. All patients had at	Included: Device manufacturer database review of patients with thoracic pain, prior unsuccessful conservative treatments including physical therapy, medication management, and minimally invasive injections ☑ Excluded: not reported Recruitment: not reported Setting: Multi-centre; academic medical centre or pain clinic (number not reported)	Primary: NRS Pain scores , lead placement, pain patterns, stimulation settings, ☑☒ Secondary: functional improvement, improved sleep, decreased medication use ☑ Measured at baseline, end of trial, at 1, 6, and 12 months after	Authors suggest a selection bias by retrospective study design and selection of 10 kHz patient responders and would miss out a large body of non-responders. Authors discuss anatomical approach to lead placement may yield better response based on high

#	Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes within scope	EAG comments
		least one lead placed in thoracic T1 – T6 region☑ Comparator: N/A		implantation, and at most recent follow up)	proportion of T1/T2 lead placement.

Key: ☑ aspect of study in scope; ☒ aspect of study not in scope ☑☒ aspect of study partially in scope, or elements of this are not in scope, † available as an abstract only.

Abbreviations: BMI, body mass index; CMM, conventional medical management; CRPS, complex regional pain syndrome; DASS, Depression, Anxiety and Stress Scale; DN4, Douleur Neuropathique; EQ-5D, EuroQol five Dimensional Questionnaire; EQ-5D-5L, EuroQol five Dimensional Questionnaire 5-level; FBSS, failed back surgery syndrome; FPS, Functional Pain Scale; GAF, Global Assessment of Functioning; GIC, Global Impression of Change; HAD, Hospital Anxiety and Depression Scale; MME, milligrams morphine equivalent; NR, not reported; NRS, numerical rating scale; PD-Q, Pain Detect Questionnaire; pDTN, Painful diabetic peripheral neuropathy; PHQ-9, 9 item Patient Health Questionnaire; PHQ-15, 15 item Patient Health Questionnaire; SF-12, Short Form Health Survey; SF-36, MOS 36 Item Short Form Health Survey; MOS-SS, Medical Outcomes Study Sleep Scale; NeppLL, neuropathic pain lower limbs; SF-MPQ-2, Short Form McGill Pain Questionnaire; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; PGIC, Patient Global Impression of Change; PGI-I, Patient Global Impression of Improvement; PSEQ, Patient Self-Efficacy Questionnaire; PSQI, Pittsburgh Sleep Quality Index; RMQD, Roland-Morris Disability Questionnaire; RMDQ-m, modified Roland-Morris Disability Questionnaire; SCS, spinal cord stimulation; SS, Subject Satisfaction; VAS, visual analogue scale; WHO-DAS 2.0, World Health Organization Disability Assessment Schedule 2.0

Appendix E – Additional outcomes

Appendix E1: Pain scores (single-arm studies)

Appendix E1a: Numerical change in pain scores (8 single arm studies)

			[n patients] Mean (SD) {95%CI} or median [IQR] pain score; p-value where reported					
Location of pain	Author (year)	Pain questionnaire used	Baseline	1 month	3 months	6 months	10 months	12 months
Back	Abraham *et al.* (2021)	VAS (cm)	[n=21] 8.52 {7.85 to 9.20}	-	-	-	-	[n=21] 4.37 {3.07-5.66} *p<0.001
	Kallewaard *et al.* (2021)	VAS (cm)	[n=58] 5.6 (1.0)	-	-	-	-	[n=50] 1.2 (1.6)
	Torres-Bayona *et al.* (2021)	VAS (cm)	[n=44] 8.1	-	-	[n=44] 4.2	-	-
	Sayed *et al.* (2020)	NRS	[n=19] 8.7 (1.3)	[n=17] 3.5 (1.5) *†p<0.001	-	[n=13] 3.5 (1.5) *†p<0.001	-	[n=9] 2.7 (1.5) *†p=0.004
	Cordero Tous *et al.* (2021)	NRS (transformed from VAS)	[n=11] 7.16	-	-	-	-	[n=11] 4.06; *p=0.003
	De Groote *et al.* (2020)	NRS	5.9 [4.5 to 7.9]	4.2 [2.9 to 4.4] *p=0.009	3.4 [2.5 to 4.5] *p=0.009	-	-	-
	DiBenedetto *et al.* (2018)	NRS	[n=30] 6.7 (1.6)	-	-	-	-	[n=30] 3.6 (2.1); *p<0.001
Leg	Kallewaard *et al.* (2021)	VAS (cm)	[n=58] 7.7 (2.4)	-	-	-	-	[n=50] 1.2 (2.0)
	Peterson *et al.* (2022b)	VAS (cm)	[n=84] 7.6 (1.6)	-	-	[n=84] 1.7 (1.9); *p<0.001	-	[n=84] 1.7 (1.8); *p<0.001
	Peterson *et al.* (2022b) ¥	VAS (cm)	[n=58] 7.4 (1.6)	-	-	[n=58] 2.0 (1.6);	-	-
	Torres-Bayona *et al.* (2021)	VAS (cm)	[n=18] 8.0	-	-	[n=18] 4.3	-	-
	Cordero Tous *et al.* (2021)	NRS (transformed from VAS)	[n=11] 8.77	-	-	-	-	[n=11] 3.45 *p=0.0001
	De Groote *et al.* (2020)	NRS	5.9 [3.6 to 7.1]	3.5 [2.4 to 5.4]	4.2 [3.4 to 5.0] *p=0.037	-	-	-
	DiBenedetto *et al.* (2018)	NRS	[n=16] 5.7 (1.7)	-	-	-	-	[n=16] 2.8 (2.0); *p=0.01
	Peterson *et al.* (2022b)	DN4	[n=77] 6.6 (1.8)	-	-	[n=77]: 3.4 (2.4); *p<0.001	-	[n=77] 3.5 (2.3); *p<0.001
	Peterson *et al.* (2022b) ¥	DN4	[n=52] 6.7 (2.1)	-	-	[n=52] 3.5 (2.4)	-	-
	Peterson *et al.* (2022b)	SF-MPQ-2 (total pain)	[n=84] 5.1 (2.0)	-	-	[n=84] 1.6 (1.6); *p<0.001	-	[n=84] 1.6 (1.7); *p<0.001
	Peterson *et al.* (2022b) ¥	SF-MPQ-2 (total pain)	[n=58] 5.6 (2.1)	-	-	[n=58] 1.5 (1.3)	-	-
	Peterson *et al.* (2022b)	SF-MPQ-2 (continuous pain)	[n=84] 5.2 (2.5)	-	-	[n=84] 1.6 (1.7); *p<0.001	-	[n=84] 1.6 (2.0); *p<0.001
	Peterson *et al.* (2022b) ¥	SF-MPQ-2 (continuous pain)	[n=58] 5.7 (2.4)	-	-	[n=58] 1.7 (1.6)	-	-
	Peterson *et al.* (2022b)	SF-MPQ-2 (intermittent pain)	[n=84] 5.4 (2.5)	-	-	[n=84] 1.7 (2.1); *p<0.001	-	[n=84] 1.5 (1.9); *p<0.001
	Peterson *et al.* (2022b) ¥	SF-MPQ-2 (intermittent pain)	[n=58] 6.0 (2.5)	-	-	[n=58] 1.4 (1.6);	-	-
	Peterson *et al.* (2022b)	SF-MPQ-2 (neuropathic pain)	[n=84]: 5.5 (2.0)	-	-	[n=84] 1.9 (1.6); *p<0.001	-	[n=84] 1.9 (1.7); *p<0.001
	Peterson *et al.* (2022b) ¥	SF-MPQ-2 (neuropathic pain)	[n=58] 5.7 (2.1)	-	-	[n=58] 1.9 (1.5)	-	-
	Peterson *et al.* (2022b)	SF-MPQ-2 (affective descriptors of pain)	[n=184] 4.0 (2.7)	-	-	[n=84] 1.1 (1.6); *p<0.001	-	[n=84] 1.0 (1.7); *p<0.001
	Peterson *et al.* (2022b) ¥	SF-MPQ-2 (affective descriptors of pain)	[n=58] 4.6 (2.7)	-	-	[n=58] 0.7 (1.1)	-	
All (back or leg)	DiBenedetto *et al.* (2018)	FPS	[n=32] 5.3 (2.0)	-	-	-	-	[n=32] 4.4 (1.9); p=0.06

†paired
¥ group crossed over from comparator arm (CMM) after 6 months of follow up. Results in this table correspond to the time of Senza implantation, with p-values omitted as they provide comparison to true baseline (prior to cross over).

			[n patients] Mean (SD) {95%CI} or median [IQR] pain score; p-value where reported					
Location of pain	Author (year)	Pain questionnaire used	Baseline	1 month	3 months	6 months	10 months	12 months
Abbreviations: CI, confidence interval; CMM, conventional medical management; DN4, Douleur Neuropathique 4; FPS, functional pain scale; IQR, interquartile range; NRS, numeric rating scale; SD, standard deviation; SF-MPQ-2, Short Form-McGill Pain Questionnaire version 2; VAS, visual analogue scale;								

Petersen *et al.* (2022b) also reported a significant improvement in Brief Pain Inventory for Painful Diabetic Neuropathy (BPI-PDN) between follow-up and baseline measurements for the Senza arm (and the cross-over arm following permanent implantation of the Senza device), however no numerical values or p-values from statistical comparisons were reported.

Appendix E1b: Percentage reduction in pain score (7 single-arm studies)

				[n patients] Percentage reduction in pain score, Mean (SD) {95%CI} or median [IQR]; p-value where reported			
Location of pain	Author (year)	Pain questionnaire used	Baseline, Mean (SD) {95% CI}	1 month	3 months	6 months	12 months
Back	Kallewaard *et al.* (2021)	VAS (cm)	[n=58] 5.60 (1.0)	[n=58] 52.0%	[n=58] 58.0%	[n=56] 53.0%	[n=50] 63.0%
	Abraham *et al.* (2021)	VAS (cm)	[n=21] 8.52 {7.85 to 9.20}	-	-	-	[n=21] 58.3% (31.0%) {44.2% to 72.4%}
	Torres-Bayona *et al.* (2021)	VAS (cm)	[n=44] 8.10	-	-	[n=44] 48.0%	-
	Kapural *et al.* (2022)	VAS (cm)	[n=83] 7.40 (1.2)		[n=68] 74.1% (25.9%)	[n=65] 72.0% (32.0%)	-
	Sayed *et al.* (2020)	NRS	[n=19] 8.70 (1.3)	[n=17], 58.6% (50.5% to 66.7%); p<0.001	-	[n=13], 58.9% (50.3% to 67.5%); p<0.001	[n=9], 70.4% (59.9% to 90.0%); p=0.004
	Cordero Tous *et al.* (2021)	NRS (transformed from VAS)	[n=11] 7.16	-	-	-	[n=11] 52.0% (28.0%)
Leg	Kallewaard *et al.* (2021)	VAS (cm)	[n=58] 7.70 (2.4)	[n=58] 76.0%	[n=58] 70.0%	[n=56] 58.0%	[n=50] 75.0%
	Torres-Bayona *et al.* (2021)	VAS (cm)	[n=18] 8.00	-	-	[n=18] 46.0%	-
	Peterson *et al.* (2022b)	VAS (cm)	[n=84] 7.60 (1.6)	-	-	[n=84] 76.0% (26.0%); p<0.001	[n=84] 77.0% (25.0%); p<0.001
	Peterson *et al.* (2022b) ¥	VAS (cm)	[n=58] 7.40 (1.6)	-	-	[n=58] *73.0%	-
	Cordero Tous *et al.* (2021)	NRS (transformed from VAS)	[n=11] 8.77	-	-	-	[n=11] 56.0% (20.0%)

*calculated by the EAG
¥ group crossed over from comparator arm (CMM) after 6 months of follow up. Results in this table correspond to the time of Senza implantation, with p-values omitted as they provide comparison to true baseline (prior to cross over).

Abbreviations: CI, confidence interval; IQR, interquartile range; NRS, numerical rating scale; SD, standard deviation; VAS, visual analogue scale

Chen *et al.* (2022) reported that the average reduction in pain over a mean follow up of 21.8 months (range 4.3 to 46.3 months) was 60.5% (SD 23.6%).

Sayed *et al*. (2020) reported variation in pain relief, related to the area being stimulated. A greater number of patients experienced pain relief through stimulation of the mid-T2 area (7/19, 36.8%), followed by low-T1 (3/19, 15.8%). Ten patients achieved greatest relief with T2 stimulation, and five with T1 stimulation. Peterson *et al*. (2021) reported that pain became worse with stimulation in 2/87 (2.0%) individual patients.

Appendix E1c: Response

Eight studies (across 10 papers) reported on response rates. The majority of studies (5/8, 55.6%), defined a response using decrease in VAS of 50% or greater when compared to baseline, 1 studies stated greater than 50%, 1 study used NPRS thresholds, 1 study used patient reported pain relief of 50% or greater (on a percentage scale, not VAS) and a DN4 of less than 4 was used in 1 study. Seven studies reported a response (based on their defined threshold) at 12 months ranging between 71.4% (Abraham *et al*. 2021) and 89.5% (Sayed *et al*. 2020) of subjects.

Location of pain	Author (year)	Time point	Pain reduction threshold	Patients meeting pain reduction threshold, n (%)
Back	Abraham *et al.* (2021)	After implantation	VAS ≥50%	18/21 (85.7%)
	Abraham *et al.* (2021)	12 months	VAS ≥50%	15/21 (71.4%)
	Kallewaard *et al*. (2021)	12 months	VAS ≥50%	38/50 (76%)
	Sayed *et al.* (2020)	12 months	VAS >50%	17/19 (*89.5%)
	Cordero Tous *et al.* (2021)	12 months	NPRS ≥5: great improvement NPRS 2 to 5: moderate NPRS <2: no improvement	2/11 (*18.2%) 6/11 (*54.5%) 3/11 (*27.3%)
Limbs	Peterson *et al*. (2022b)	6 months	VAS ≥50%	*72/84 (85.7%)
	Peterson *et al*. (2022b) ¥	6 months	VAS ≥50%	*49/58 (84.5%)
	Kallewaard *et al*. (2021)	12 months	VAS ≥50%	40/50 (80%)
	Peterson *et al*. (2022b)	12 months	VAS ≥50%	*72/84 (85.7%)
	Peterson *et al*. (2022b)	6 months	DN4 <4	*38/77 (49.0%)
	Peterson *et al*. (2022b)	12 months	DN4 <4	*38/77 (49.0%)
	Peterson *et al*. (2022b) ¥	6 months	DN4 <4	*28/52 (54.0%)
	Cordero Tous *et al.* (2021)	12 months	NPRS ≥5: great improvement NPRS 2 to 5: moderate NPRS <2: no improvement	7/11 (63.6%) 3/11 (27.3%) 1/11 (9.1%)
Lower back and lower limbs (not reported separately)	Chen *et al*. (2022)	Last visit (mean: 21.8 months)	Patient reported pain relief ≥50%	58/73 (79.5%)
		12 months	Patient reported pain relief ≥50%	50/59§ (84.7%)
		24 months	Patient reported pain relief ≥50%	24/27§ (88.9%)
		1 month	VAS ≥50%	*39/62 (63.0%)

Location of pain	Author (year)	Time point	Pain reduction threshold	Patients meeting pain reduction threshold, n (%)
	Torres-Bayona *et al*. (2021)	6 months	VAS ≥50%	*48/62 (77.0%)
	Kapural *et al*. (2022)	3 months	VAS ≥50%	55/68 (80.9%; †74.3%)
		6 months	VAS ≥50%	52/65 (80.0%)
		12 months	VAS ≥50%	50/64 (78.2%)

*calculated by the EAG; †intention to treat analysis; § Denominator changes due to availability of patient data for follow up at each time point; ¥ group crossed over from comparator arm (CMM) after 6 months of follow up. Results in this table correspond to the time of Senza implantation, with p-values omitted as they provide comparison to true baseline (prior to cross over).

Abbreviations: DN4, Douleur Neuropathique; NPRS numerical pain rating scale; VAS, visual analogue scale

Appendix E1d: Remission

Two studies reported on remission rates, however both applied a different threshold (less than or equal to 2.5 cm or 3.0 cm on the Visual Analogue Scale) and at different follow-up time points.

Location of pain	Author (year)	Time point	Pain reduction threshold	Patients meeting pain reduction threshold, n (%)
Back	Kallewaard *et al*. (2021)	12 months	VAS ≤ 2.5cm	40/50 (80%)
Limb	Petersen *et al.* (2021)	3 months	VAS ≤ 3.0cm	69/88 (78.4%)
	Petersen *et al.* (2021)	6 months	VAS ≤ 3.0cm	53/88 (60.2%)
	Kallewaard *et al*. (2021)	12 months	VAS ≤ 2.5cm	34/50 (68%)
Abbreviations: VAS, visual analogue scale				

Appendix E2: Patient satisfaction (single arm studies)

Location of pain	Author (year)	Scoring system	Time point	Intervention
Back	Kallewaard *et al*. (2021)	PGI-I	12 months	"Very much" or "much" improved: 72.0% (36/50)
	Cordero Tous *et al*. (2021)	PGI-I	12 months	"Very much improvement" or "much improvement": 54.0% (6/11)
Limb	Peterson *et al*. (2022b)	PGI-I	6 months	"Better" or "A great deal better": 67.0% (*56/84) "Little, somewhat or moderately better": 32.0% (*27/84) "No change", or "Almost the same": 1.0% (*1/84)
	Peterson *et al*. (2022b) ¥	PGI-I	6 months	"Better" or "A great deal better": 71.0% (41/58) "Little, somewhat or moderately better": 28.0% (16/58) "No change", or "Almost the same": 2.0% (1/58)
	Peterson *et al*. (2022b)	PGI-I	12 months	"Better" or "A great deal better": 73.0% (61/84) "Little, somewhat or moderately better": 23.0% (19/84) "No change", or "Almost the same": 5.0% (4/84)
	Cordero Tous *et al*. (2021)	PGI-I	12 months	"Very much improvement" or "much improvement": 72.0% (8/11)
Lower back and lower limbs (not reported separately)	Kapural *et al*. (2022)	PGI-I	6 months	"Better" or "A great deal better": 70.8% (*46/65) "Little, somewhat or moderately better": 24.7% (*16/65) "No change", or "Almost the same": 4.6% (*3/65)
Back	Kallewaard *et al*. (2021)	Patient reported satisfaction	12 months	"Satisfied" or "Very satisfied": 86% (43/50)

¥ group crossed over from comparator arm (CMM) after 6 months of follow up. Results in this table correspond to the time of Senza implantation, with p-values omitted as they provide comparison to true baseline (prior to cross over).
* calculated by the EAG
Abbreviations: CMM, conventional medical management; PGI-I, Patient Global Impression of Improvement

Appendix E3: Quality of life (single arm studies)

Location of pain	Author (year)	Scoring system	Intervention, [n patients] Mean (SD) {95% CI}	Statistical comparison **with baseline**, p-value
Back	Kapural *et al*. (2022)	EQ-5D-5L index score	Baseline: [n=68] 0.579 Follow up (3 months): [n=68] 0.786 Follow up (6 months): [n=65] 0.782	 NR NR
	Kapural *et al*. (2022) ¥	EQ-5D-5L index score	Baseline: NR Follow up (3 months): [n=55] improvement of 0.179 (0.131) Follow up (6 months): [n=55] improvement of 0.182 (0.135)	 NR NR
	Kallewaard *et al*. (2021)	PCS	Baseline: 22.9 (1.4) Follow up (1 month): 14.5 (1.3) Follow up (6 months): 12.7 (1.7) Follow up (12 months): 14.8 (1.7)	 NR NR NR
		HADS anxiety	Baseline: 6.0 Follow up (1 month): 3.6* Follow up (6 months): 4.1* Follow up (12 months): 3.8*	 NR NR NR
		HADS depression	Baseline: 6.9 Follow up (1 month): 4.0* Follow up (6 months): 4.1* Follow up (12 months): 3.7*	 NR NR NR
Limb	Peterson *et al*. (2022b)	EQ-5D-5L VAS	Baseline: [n=84] 58.7 (18.7) Follow up (6 months): [n=84] 73.3 (16.1) Follow up (12 months): [n=84] 75.6 (18.6)	 <0.001 <0.001
	Peterson *et al*. (2022b) ¥	EQ-5D-5L VAS	Baseline: [n=57] 56.8 (20.3) Follow up (6 months): [n=57] 75.4 [14.6]	
	Peterson *et al*. (2022b)	EQ-5D-5L index score	Baseline: [n=104] 0.644 (0.145) Follow up (6 months): [n=84] 0.767 (0.131) Follow up (12 months): [n=84] 0.780 (0.123)	 <0.001 <0.001

Location of pain	Author (year)	Scoring system	Intervention, [n patients] Mean (SD) {95% CI}	Statistical comparison **with baseline**, p-value
	Peterson *et al*. (2022b) ¥	EQ-5D-5L index score	Baseline: [n=57] 0.604 (0.144) Follow up (6 months): [n=57] 0.761 (0.087)	
	Peterson *et al*. (2022b)	Diabetes Quality of Life – satisfaction	Baseline: [n=83] 3.0 (0.7) Follow up (6 months): [n=83] 2.2 (0.8) Follow up (12 months): [n=83] 2.0 (0.8)	 <0.001 <0.001
	Peterson *et al*. (2022b) ¥	Diabetes Quality of Life – satisfaction	Baseline: [n=58] 3.2 (0.7) Follow up (6 months): [n=58] 2.2 (0.8)	
	Peterson *et al*. (2022b)	Diabetes Quality of Life – impact	Baseline: [n=83] 2.5 (0.7) Follow up (6 months): [n=83] 1.9 (0.7) Follow up (12 months): [n=83] 1.8 (0.6)	 <0.001 <0.001
	Peterson *et al*. (2022b) ¥	Diabetes Quality of Life – impact	Baseline: [n=58] 2.7 (0.6) Follow up (6 months): [n=58] 1.9 (0.5)	
	Peterson *et al*. (2022b)	Diabetes Quality of Life – worry (social or vocational)	Baseline: [n=83] 1.7 (0.7) Follow up (6 months): [n=83] 1.4 (0.6) Follow up (12 months): [n=83] 1.4 (0.6)	 <0.001 <0.001
	Peterson *et al*. (2022b) ¥	Diabetes Quality of Life – worry (social or vocational)	Baseline: [n=58] 1.7 (0.7) Follow up (6 months): [n=58] 1.3 (0.4)	
	Peterson *et al*. (2022b)	Diabetes Quality of Life – worry (diabetes-related)	Baseline: [n=83] 2.1 (0.8) Follow up (6 months): [n=83] 1.8 (0.8) Follow up (12 months): [n=83] 1.6 (0.7)	 <0.01 <0.001
	Peterson *et al*. (2022b) ¥	Diabetes Quality of Life – worry (diabetes-related)	Baseline: [n=58] 2.4 (0.9) Follow up (6 months): [n=58] 1.8 (0.7)	
	Peterson *et al*. (2022b)	Diabetes Quality of Life – total	Baseline: [n=83] 2.5 (0.6) Follow up (6 months): [n=83] 1.9 (0.6) Follow up (12 months): [n=83] 1.8 (0.6)	 <0.001 <0.001
	Peterson *et al*. (2022b) ¥	Diabetes Quality of Life – total	Baseline: [n=58] 2.7 (0.6) Follow up (6 months): [n=58] 1.9 (0.5)	
Lower back and lower	De Groote *et al*. (2020)	PSQI	Baseline: NR Follow up (3 months): NR	0.24

Location of pain	Author (year)	Scoring system	Intervention, [n patients] Mean (SD) {95% CI}	Statistical comparison **with baseline**, p-value
limbs (not reported separately)		PCS	Baseline: NR Follow up (3 months): NR	0.05

* calculated by EAG from available data to maintain consistency of reporting across table
¥ group crossed over from comparator arm (CMM) after 6 months of follow up. Results in this table correspond to the time of Senza implantation, with p-values omitted as they provide comparison to true baseline (prior to cross over).

Abbreviations: CI, confidence interval; CMM conventional medical management; EQ-5D-TTO, EuroQol five Dimensional Questionnaire Time Trade Off; EQ-5D-5L, EuroQol five Dimensional Questionnaire 5-level; EQ-5D-5L VAS, EuroQol five Dimensional Questionnaire 5-level visual analogue scale; HADS, Hospital Anxiety and Depression Scale; NR, not reported; PCS, Pain Catastrophizing Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SF-36, MOS 36 Item Short Form Health Survey

Peterson *et al.* (2021, 2022a, 2022b) all reported an improvement in sleep quality at 12 months post-implantation in approximately 60% of patients. Improvements in sleep were also reported by Sayed *et al.* (2020) in 73.7% (14/19) of patients, Chen *et al*. (2022) in 78.5% (51/65) of patients, and Abraham *et al*. (2021) in 76.5% (13/17) of patients.

Kallewaard *et al*. (2021) reported that reductions in Pain Catastrophizing Scale (PCS) were consistent across the three subscales (helplessness, magnification, and rumination) at 1, 6 and 12 months post-implantation when compared with baseline.

Appendix E4: Functional disability measures (single arm studies)

Location of pain	Author (year)	Scoring system	Intervention, Mean (SD) {95% CI}	Statistical comparison **with baseline**, p-value
Back	Kapural *et al*. (2022)	ODI	Baseline: 46.8 Follow up (3 months): 22.6 Follow up (6 months): 24.1 Follow up (9 months): 24.0 Follow up (12 months): 24.0	 NR NR NR NR
	Kallewaard *et al*. (2021)	ODI	Baseline: 52.4 Follow up (1 month): 33.3 Follow up (6 months): 32.7* Follow up (12 months): 27.1*	 NR NR NR
	Cordero Tous *et al*. (2021)	FRI – pain intensity	Baseline: 3.36 Follow up (12 months): 1.45	 NR
		FRI – sleeping	Baseline: 3.00 Follow up (12 months): 1.27	 NR
		FRI – personal care	Baseline: 2.00 Follow up (12 months): 1.54	 NR
		FRI – travel	Baseline: 3.18 Follow up (12 months): 2.00	 NR
		FRI – work	Baseline: 3.27 Follow up (12 months): 2.54	 NR
		FRI – recreation	Baseline: 3.63 Follow up (12 months): 2.81	 NR
		FRI – pain	Baseline: 3.45 Follow up (12 months): 2.17	 NR
		FRI – lifting	Baseline: 2.81 Follow up (12 months): 2.18	 NR
		FRI – walking	Baseline: 3.54 Follow up (12 months): 1.45	 NR
		FRI – standing	Baseline: 3.00 Follow up (12 months): 1.90	 NR
		WHODAS 2.0	Baseline: 1.97 (0.42)	

Location of pain	Author (year)	Scoring system	Intervention, Mean (SD) {95% CI}	Statistical comparison **with baseline**, p-value
	DiBenedetto *et al*. (2018)		Follow up (12 months): 1.92 (0.64)	0.57
		RMDQ-m	Baseline: 13.9 (4.5) Follow up (12 months): 10.8 (4.8)	0.02
Leg	Peterson *et al*. (2021)	GAF	Baseline: NR Follow up (time point not reported): 17.7 point improvement {13.8 points to 21.6 points}	NR

* calculated by EAG from available data to maintain consistency of reporting across table

Abbreviations: CI, confidence interval; EQ-5D-TTO, EuroQol five dimension scale questionnaire Time trade off; EQ-5D-5L, EuroQol five Dimensional Questionnaire 5-level; EQ-5D-5L VAS, EuroQol five Dimensional Questionnaire 5-level visual analogue scale; FRI, Functional Rating Index; GAF, Global Assessment of Functioning; N/A, not applicable; NR, not reported; ODI, Oswestry Disability Index; PSQI, Pittsburgh sleep quality index; RMDQ-m modified Roland Morris Disability Questionnaire, SD, standard deviation; SF-36, 36 Item Short Form Health Survey, WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0.

Kapural *et al.* (2022) also reported on the proportion of ODI responders (at least ten-point reduction in ODI score) which was 80.9% at 3 months, and 78.5% at 12 months, although this was reported as 78.1% elsewhere in the paper. Kallewaard *et al*. (2021) reported that 62.0% (31/50) of patients reduced their ODI score enough to be reclassified from “severely disabled or crippled” to “moderately or minimally disabled”. Cordero Tous *et al*. (2021) reported an average improvement on the Functional Rating Scale of 28.4% (95% CI: 21.19% to 35.62%; p=0.0001). Functional improvements were also reported by 76.0% (57/75) of patients in Chen *et al*. (2022), and 84.2% (16/19) patients in Sayed *et al*. (2020). Abraham *et al*. (2021) also reported improvements of daily living in 76.5% (13/17) of patients, by 12 months.

Appendix E5: Opioid and other analgesia use (single arm studies)

Location of pain	Author (year)	Time point	Baseline opioid use	Increase	Decrease	Discontinued	No change	No data
Back and leg	Cordero Tous *et al*. (2021) [£]	12 months	72.2% (13/18)	9.0% (n=1)	45.0% (n=5)	36.0% (n=4)	45.0% (n=5)	-
Back and leg	DiBenedetto *et al*. (2018)	12 months	65.6% (21/32)	4.8% (n=1)	71.4% (n=15)	-	23.8% (n=5)	-
Back and leg	Kallewaard *et al*. (2021) [£]	12 months	50.0% (29/58)	-	7.0% (n=2)	24.0% (n=7)	-	-
Back	Sayed *et al*. (2020)	NR	*NR	-	47.4% (n=9)	-	26.3% (n=3)	26.3% (n=3)
Back and leg	Kapural *et al*. (2022)	6 months	52.1%	6.0%	44.0% (n=32)	21.9% (n=7)	28.0%	-
Back and leg	Abraham *et al*. (2021)	12 months	*76.2% (16/21)	6.3% (n=1)	43.8% (n=7)	-	50.0% (n=8)	-

*analgesia type not reported
[£] unclear or incomplete reporting of percentages, and EAG unable to correct.

Abbreviations: NR, not reported

Kapural *et al.* (2022) reported that mean daily opioid intake in those receiving opioids decreased by a mean of 45.8% between baseline and 6 months. DiBenedetto *et al*. (2018) reported that 23.8% (5/21) subjects had dose reductions of at least 60% at 12 months, including one who was no longer using opioids. They also reported a significant reduction in mean opioid dose of 26.2 (standard deviation: 32.8) MME between baseline and 12 months follow up (p=0.001). Kallewaard *et al*. (2021) reported that the proportion of patients taking opioids at safe doses (that is, none, as needed, or less than 50 mg a day) increased to 80% at 12 months.

Appendix F – Ongoing trials

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
PDN Post market, multicentre, prospective global clinical study (PDN-PM) NCT05301816 US	Status: Active, Recruiting (last updated 30 June 2022) Interventional trial (single arm) Estimated Start date: July 2022 Estimated Primary completion date: October 2024 Estimated Study completion date: March 2026 Sponsor: Nevro Corp	Estimated enrolment: 497 Inclusion criteria: • Have been clinically diagnosed with diabetes, according to the local country diabetes association guidelines, as well as painful diabetic neuropathy (PDN) of the lower limbs refractory to conventional medical management. • Average pain intensity (over the last 7 days) of ≥5 out of 10 cm on the Visual Analog Scale (VAS) in the lower limbs at enrollment/baseline. • The clinical decision has been made to provide treatment using the Nevro Spinal Cord Stimulation that includes 10 kHz therapy prior to enrollment in the study. • Be willing and capable of giving written informed consent. • Be willing and able to comply with study-related requirements and procedures and attend all scheduled visits. Exclusion Criteria: • Have a diagnosis of a lower limb mononeuropathy (e.g., causalgia and tibial or peroneal neuropathies), have had a lower limb amputation other than toes, or have large (≥3 cm) and/or gangrenous ulcers of the lower limbs • Have a medical condition or diagnosis that is inconsistent with Nevro's SCS System guidelines in	• Trial success rate/responder rate [2 weeks]. • Patient-reported overall pain relief [12 months]. • Leg pain [12 months] • Quality of life [12 months] • Pain inventory [12 months] • Global impression of change in health status [12 months]	• Patients work status [12 months] • Device safety [12 months]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
		the Physician's Manual for the relevant country, or as per standard clinical practice. • Have a medical condition or pain in other areas, not intended to be treated in this study, that could interfere with study procedures, accurate pain reporting, and/or confound the evaluation of study endpoints, as determined by the Investigator (such as primary headache, fibromyalgia, post-herpetic neuralgia, osteoarthritis, peripheral vascular disease, or small vessel disease).		
Comparing Long-term Effectiveness of high Frequency and Burst Spinal Cord stimulation NCT03681262 US	Status: Active, Recruiting (last updated: 05 May 2022) RCT; High Frequency spinal cord stimulation compared to Burst spinal cord stimulation Estimated Start date: August 2019 Estimated Primary completion: December 2023 Estimated Study completion: December 2026	Estimated enrolment: 160 Inclusion criteria: • Adult English-speaking patient 18 years old or above • Persistent pain in lower back and/or leg for more than six months • Candidate for spinal cord stimulation (with either high frequency or burst waveforms) based on recommendations from Stanford Pain Management Center Neuromodulation Multidisciplinary Team Conference. Exclusion criteria: • Motor weakness in neurological examination in lower body based on the assessment by treating pain physicians • Previous failed spinal cord stimulation trial with either high frequency or burst waveforms • Patient refusal	• Change in pain intensity [12 months]	• Patient global impression of change [12, 24 and 36 months] • Pain Intensity [12, 24 and 36 months] • Function [12, 24 and 36 months] • Pain Interference [12, 24 and 36 months] • Depression [12, 24 and 36 months] • Anxiety [12, 24 and 36 months]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
	Sponsor: Stanford University			
Comparison of 10 kHz SCS Combined With CMM to CMM Alone in the Treatment of Neuropathic Limb Pain (SENZA-PDN) NCT03228420 US [12 months results in Petersen *et al.* 2022b]	Status: Active, not recruiting (last updated 10 August 2021) RCT: Senza 10 kHz SCS + CMM, compared to CMM alone Estimated completion date: December 2022 Sponsor: Nevro Corp	Target/actual enrolment: 430 Inclusion criteria: • Have been clinically diagnosed with painful diabetic neuropathy (PDN) of the lower limbs. • Average pain intensity of ≥ 5 out of 10 cm on the VAS in the lower extremities at enrollment. • Have stable neurological status. • Be on a stable analgesic regimen. • Be 22 years of age or older at the time of enrollment. • Be an appropriate candidate for the surgical procedures required in this study. • Be capable of subjective evaluation, able to read and understand English-written questionnaires, and able to read, understand and sign the written informed consent in English. • Be willing and capable of giving informed consent. • Be willing and able to comply with study-related requirements, procedures, and scheduled visits. Exclusion criteria: • Have a diagnosis of a lower limb mononeuropathy, have had a lower limb amputation, or have large (≥3 cm) and/or gangrenous ulcers of the lower limbs. • Have a BMI ≥ 40. • Currently prescribed a daily opioid dosage >120 mg morphine equivalents. • Have a medical condition or pain in other area(s), not intended to be treated in this study. • Have a current diagnosis of a progressive neurological disease such a multiple sclerosis,	• Composite of safety and efficacy [3 months]	• Pain of 3 or less [3 months]; • Crossover rates [6 months]; • Responder rates [6 months]; • Remitter rates [6 months]; • Neurological assessment [3 months, 6 months]; • Health-related Quality of Life [6 months]; • Haemoglobin A1c [6 months]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
		chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, brain or spinal cord tumour, central deafferentation syndrome, Complex Regional Pain Syndrome, acute herniating disc, severe spinal stenosis and brachial plexus injury. • Have a current diagnosis or condition such as a coagulation disorder, bleeding diathesis, platelet dysfunction, low platelet count, severely diminished functional capacity due to underlying cardiac/pulmonary disease, symptomatic uncontrolled hypertension, progressive peripheral vascular disease or uncontrolled diabetes mellitus that presents excess risk for performing the procedure. • Have failed prior SCS, dorsal root ganglion (DRG) stimulation, or peripheral nerve stimulation (PNS) trials for chronic intractable pain. • Have significant spinal stenosis, objective evidence of epidural scarring and/or any signs or symptoms of myelopathy. • Any previous history of surgery on the posterior elements (laminectomy, posterior fusion) resulting in a compromised epidural space. • Be benefitting from an interventional procedure and/or surgery to treat lower limb pain. • Have an existing drug pump and/or another active implantable device such as a pacemaker. • Have a condition currently requiring or likely to require the use of diathermy or MRI that is inconsistent with Senza system guidelines in the Physician's Manual. • Have either a metastatic malignant neoplasm or untreated local malignant neoplasm. • Have a life expectancy of less than one year.		

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
		• Have a local infection at the anticipated surgical entry site or an active systemic infection. • Be pregnant or plan to become pregnant during the study. Women of childbearing potential who are sexually active must use a reliable form of birth control, be surgically sterile, or be at least 2 years post-menopausal. • Have within 6 months of enrollment a significant untreated addiction to dependency producing medications, alcohol or illicit drugs. • Be concomitantly participating in another clinical study. • Be involved in an injury claim under current litigation. • Be a recipient of Social Security Disability Insurance (SSDI). • Have a pending or approved worker's compensation claim. • Have evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention and/or ability to evaluate treatment outcome.		
Sham-controlled RCT on 10kHz High-frequency Spinal Cord Stimulation for Chronic neuropathic low back Pain (Modulate-LBP) NCT03470766	Status: Unknown (Last updated 05 October 2018) RCT; Nevro Senza system (HF10 Therapy) compared to sham-device Estimated primary	Estimated Enrolment: 96 Inclusion Criteria: • Adults over the age of 18 • Onset of low back pain >12 months • Low back pain intensity >60 out of 100mm on pain visual analogue scale (VAS) • Presence of clear component of neuropathic pain based on a PainDETECT Questionnaire score of >19 (we will monitor this inclusion criteria in the early stage of the trial and revise if necessary)	• Mean VAS Back Pain (7 Day Subject VAS Pain Diary) [6 months post randomisation]	• Oswestry disability index (v2.1a) [1, 3, and 6 months post randomisation] • PHQ-9 Questionnaire [1, 3, and 6 months post randomisation] • PSQI Questionnaire [1, 3,

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
UK [Trial protocol published Al-Kaisy *et al.* 2020]	completion date: August 2020 Estimated study completion date: August 2020 Sponsor: Guy's and St Thomas NHS Foundation Trust; Pain and Neuromodulation Academic Research Centre (PANARC); University of Exeter; NIHR, King's College London, University of Oxford; University of Liverpool; James Cook University Hospital	• Degenerative disc disease confirmed by imaging or internal disc disruption as confirmed by discography • On stable pain medications, as determined by the Investigator, for at least 28 days prior to enrolling in this study and not change medication dosage without consulting Investigator • Legally able to provide informed consent • Able to comply with study-related requirements, procedures and visits Exclusion Criteria: • Had previous spinal surgery • Chronic widespread pain • Subject has an active implanted device, whether turned on or off (e.g. pacemaker, intrathecal pump, deep brain stimulator etc.) • A current diagnosis of a progressive neurological disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, rapidly progressive diabetic peripheral neuropathy, brain or spinal cord tumour, or severe/critical central or foraminal spinal stenosis • Mechanical spine instability detected by a clinician (validation by flexion/extension films of lumbar spine within the past 6 months showing 4 mm or more translational movement or excessive angular movement manifested by >5 degrees segmental angular movement) e.g. any forms of spondylolisthesis • A medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or		and 6 months post randomisation] • PGIC Questionnaire [1, 3, and 6 months post randomisation] • EQ-5D Questionnaire [1, 3, and 6 months post randomisation] • Medication Usage [1, 3, and 6 months post randomisation] • Sensation Map [1, 3, and 6 months post randomisation] • Healthcare utilisation, work status, work absence, and out of pocket expenses [6 months post randomisation]. • Safety/Adverse Events [6 months post randomisation]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
		confound evaluation of study endpoints, as determined by the Investigator • Bleeding diathesis such as coagulopathy or thrombocytopenia • Immunocompromised and at an increased risk for infection • Systemic infection or local infection that would contraindicate SCS placement • Metastatic malignant disease or active local malignant disease • Pregnant (if female and sexually active, subject must be using a reliable form of contraception, be surgically sterile or be at least 2 years post-menopausal) • Active alcohol, marijuana, recreational or prescription drug abuse or dependence or unwilling to stop/reduce excessive inappropriate medication. • Evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance of intervention and/or ability to evaluate treatment outcome as determined by the Investigator • Concomitant participation in another clinical trial (surgery, device or drug)		
A Prospective, Open Label, Pilot Study of Patient OutcoMes Following Successful TriAl of High Frequency SpInal CorD Stimulation at 10kHz	Status: Unknown (last updated: 15 January 2019 recruitment was active, not recruiting) Interventional (single arm)	Estimated enrolment: 25 Inclusion Criteria: • Patient is 18 years of age or older and has given written informed consent. • Has persistent chronic predominant low back pain of neuropathic origin, with or without radiculopathy, for a minimum of 6 months	• 50% reduction in patient reported Visual analogue scale for pain [12 months	• 50% reduction in patient reported numerical rating score for pain [12 months compared to baseline]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
(HF10™) Leading to Permanent Implant Compared to Trial Failure and Standard CarE for the TreatmeNt of Persistent Low BACK Pain of Neuropathic Origin (Maiden Back) NCT02689375 UK	Estimated primary completion date: October 2017 Estimated study completion date: October 2021 Sponsor: Leeds Teaching Hospitals NHS trust	• Visual Analogue Scale (VAS) back pain score of at least 50 mm at baseline • Confirmation of pain from neuropathic origin by SLANSS score (≥12) AND PainDETECT score (≥19) • Total daily dose of opioids equivalent to ≤200mg of Morphine • No previous open spinal surgery (percutaneous procedures such as nucleoplasty are not considered as open surgical procedures) • Failed conservative therapies such as physiotherapy, chiropractor, hydrotherapy, TENS. • MRI within the previous 18 months (as per standard care) • In the investigators opinion the patient is a suitable candidate for HF10. Exclusion Criteria: • Patient has mechanical spine instability based on flexion/extension testing of lumbar spine (documented in the last 6 months) • Patient is pregnant, or pregnancy is suspected or planned within the first six months of the study timeframe. • Patient has a cardiac pacemaker, automatic defibrillator, or any other implanted device, which will make the trial impossible. • Allergy to device components or drugs to be used in the intended procedure. • Medical co-morbidities that preclude surgical intervention. • Patient is incapable of understanding or responding to the study questionnaires	compared to baseline]	

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
		• Patient is incapable of understanding or operating the patient programmer handset. • History of previous open spinal surgery (not percutaneous procedures) • Patient is morbidly obese (BMI ≥ 40). • Patient is simultaneously participating in another device or drug study within the last 30 days. • Patient has a spinal fracture, tumour or infection. • Clinical evidence of cauda equina syndrome. • Progressive neurologic deficit.		
Comparison of Continuous and Burst high Frequency Spinal Cord Stimulation Paradigms NCT04709757 Study location: NR	Status: Not yet recruiting (Last updated: 28 May 2021) Estimated Primary Completion date: March 1st 2023 Cross-over RCT; Intermittent dosing HF10 (30/90) compared with HF10 (30/360) Estimated Study completion date: March 2023 Sponsor: Rush University Medical Centre	Estimated Enrolment: 30 Inclusion Criteria: • Age between 18 and 90 • 1-year or more use of continuous HF10 therapy as delivered a permanently implanted Nevro Omnia Neurostimulation System for chronic back and/or leg pain • Some level of decreasing pain relief from their SCS system (see fig. 3) • Willing and able to complete protocol requirements Exclusion Criteria: • Previous intermittent dosing usage and/or failure • Cervical SCS system • Other concurrent neuromodulation system in place • Current daily morphine milligram equivalent usage 90mg or higher	• Numeric Rating Scale pain scores [Up to 3 months]	• Patient Satisfaction with Treatment Score [Up to 3 months] • Chronic Pain Acceptance Questionnaire (CPAQ-8) [Up to 3 months] • Current mode of stimulation [Up to 3 months] • Stimulator settings - frequency [Up to 3 months] • Stimulator settings - amplitude [Up to 3 months] • Stimulator settings - pulse width [Up to 3 months]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
				• Charging frequency of spinal cord stimulator [Up to 3 months] • PROMIS-Fatigue 8 questionnaire [Up to 3 months] • PROMIS-Sleep Disturbance 4a questionnaire [Up to 3 months] • PROMIS-Emotional Distress- 8a Anxiety questionnaire [Up to 3 months] • PROMIS- Physical Function 8b questionnaire [Up to 3 months] • PROMIS- Pain Interference 6b questionnaire [Up to 3 months] • PROMIS-Global Health 10 item questionnaire [Up to 3 months] • PHQ-8 [Up to 3 months] • Patient Global Impression of Change [Up to 3 months]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Abbreviations: BMI, Body Mass Index; BPI-DPN, Brief pain inventory for diabetic peripheral neuropathy; CGIC, Clinician Global Impression of Change; CMM, Conventional Medical Management; NR, not reported; PGIC, Patient Global Impression of Change; PDN, Painful Diabetic Neuropathy; PGIC, Patients' Global Impression of Change (PGIC), PHQ 9, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; PROMIS, Patient-Reported Outcome Measures Information System (PROMIS); RCT, randomised controlled trial; SCS, spinal cord stimulation; VAS, visual analogue scale;				

Appendix G – Correspondence Log

Appendix G1 – Communication with Company

#	Question	Answer (responses received 30/08/22)
1.	Please can you provide update to date regulatory information including CE certification, declaration of conformity, and instructions for use for Senza I, Senza II and Senza Omnia?	Please find attached the current CE mark and the DoC and the Physician Implant Manual covering Senza, Senza II and Senza Omnia.
2.	If needed, can Senza be switched by the user or healthcare professional from HF10 therapy to lower frequency therapy?	Yes, Senza is the only product line that delivers 10,000 Hz independently or in combination with low frequency (2Hz to 1,200 Hz).
3.	Senza Omnia is stated as having additional digital modes/settings, can you please provide more detail on what these are?	Senza Omnia can be considered as a software expansion providing increased versatility in programming using combined frequencies and waveforms.
4.	Are there any other differences between Senza Omnia and its predecessors that we should be aware of?	Senza is a product family covering Senza, Senza II and Senza Omnia (our latest and current version) – a logic product evolution. Senza Omnia has improved versatility and flexibility of programming options and software updating capabilities.
#	Further questions (sent 31/08/22)	Answer (responses received 03/09/2022)
1.	You have sent the DoC and Design Examination Certificate. For completeness, could you also please send the Full Quality Assurance Certificate detailed below please? [screenshot redacted for simplicity]	Please find attached the requested certificate. [Attachment received]
2.	We note that the Physician Implant Manual mentions, on page 25, the Surgical Lead Manual. Would it be possible for us to have a copy of this too please?	Please find attached the Surgical Lead Manual “Surpass” and “Surpass-C”. [Attachment received]
3.	We would like to understand more about the new digital modes and settings available with Senza Omnia, is there perhaps a user guide that covers these?	Senza Omnia was a development of the Senza range incorporating feedback from patients and physicians which enables the use of the full range of waveforms (2Hz – 1,200Hz and 10kHz) and the use of waveforms in combination. This offers users increased versatility and flexibility of treatment. Please find attached our patient manual “Senza System”, Senza-Bluetooth-Trial-System” and the information for prescribers (Senza-Bluetooth-Trial-System). [Attachments received]
4.	We understand there have been changes to the charging port	The change in the charging port is a technical development which does not influence

	between different Senza devices, and wondered if you could share any further information on this. Again, if there is a patient user guide that covers this, it would be helpful for us to have a copy please.	the functionality and the use of Omnia Senza. Please see the attached references. [Attachments received]

Appendix G2 – Communication with Clinical Experts

Sent to 3 Clinical Experts 22/08/2022, responses received from 3 out of 3.

#	Question	Answer
1.	Are High-Dose and High-Density Spinal Cord Stimulation (SCS) different modalities to High frequency-10kHz SCS? a. Under what circumstances/criteria would they each be used	**Expert 1**: Yes predominately the HF10 Senza would be used for back and leg pain /diabetic neuropathy/upper limb and headache. The mechanism of action is not fully understood for all of these wave forms
		Expert 2: High-dose and high-density spinal cord stimulator are completely different to high-frequency spinal cord stimulator. They are variation of the conventional spinal cord stimulator and are all paraesthesia- free spinal cord stimulator, working at conventional frequency. Both these waveform are available in conventional spinal cord stimulator battery such as the Medtronic Intellis platform. They are typically used in patients with failed back surgery syndrome with back and leg pain.
		Expert 3: Yes they are different therapies. High density is 10-1200Hz, Senza is 10000Hz (Under what circumstances/criteria would they each be used?) Patient or clinician preference. Support and programming availability. Both work.
2.	The EAG has identified the following low-frequency SCS devices. Which of these are you aware of being used in the NHS? Are there any others the EAG has missed? • Medtronic: - RestoreSensor (2Hz-1200Hz) - Intellis (DTM 10Hz-1200Hz) - PrimeAdvanced (2Hz-130Hz?)	**Expert 1**: [expert added Itrel , Saluda Evoke and Stimwave]

#	Question	Answer
	- Synergy Versitrel (1Hz-1200Hz) - Restore Ultra (2Hz-1200Hz) - Vanta (DTM, 1200Hz) • Abbott: - Prodigy (Burst DR, 0Hz-1200Hz) - Proclaim XR Recharge (Burst DR, 0Hz-1200Hz) - Proclaim XR Recharge free (Burst DR) • Boston Scientific: - Precision Novi (1kHz) - Montage (0-1200Hz) - WaveWriter Alpha (2Hz-1200Hz) • St Jude Medical - EonTM IPG (1200Hz)	**Expert 2:** [expert indicated St Jude is now Abbott, added Saluda Evoke and Stimwave] **Expert 3:** [expert indicated awareness of all devices, added no new devices]
3.	The EAG was unable to identify any high-frequency (10kHz or above) SCS devices, other than Senza. Are you aware of any other high-frequency devices the EAG may have missed?	**Expert 1:** No the only devices I am aware of 10HZ is currently available is Nevro Senza **Expert 2:** Currently, none of the other companies are able to use the high-frequency waveform. It has been patented by NEVRO. **Expert 3:** Senza is the only 10kHz SCS system available commercially (others are used experimentally). High frequency is anything over 500Hz
4.	Is Senza (I, II, Omnia) typically used only for high-frequency treatment, or are you aware of it being used for low-frequency treatment? a. If it is also routinely used at low-frequency, are you able to estimate approximate proportions for low- and high-frequency use? b. Would treatment ever be switched from high- to low-frequency, and if so, in what	**Expert 1:** Yes predominately High Frequency it can be used for low frequency programme a. Senza would be inserted for high frequency If the patient returns with reduced efficacy we may do further programming to include a low frequency We Approximate small proportion of this occurring in our service. b. Small proportion unable to give accurate numbers c. The device would be fitted for high HF10 as this is not the device of choice for low frequency d. Yes occasionally this is done

#	Question	Answer
	proportion of cases might this occur? c. What about switching from low- to high-frequency? d. Would patients ever receive both low- and high-frequency SCS in the same treatment programme, or is it one or the other?	**Expert 2:** Senza 1, Senza II and Omnia are typically used for high-frequency treatment. However, in patients where high-frequency is not giving adequate pain relief, there is an option to try the low frequency waveform which is built into the IPG. However, it is not used routinely unless needed. Majority of the patients are still using high-frequency waveform. Approximately 10-20% of patients with high-frequency device may need low-frequency waveform. Alternatively, 10-20% of patients who were implanted with conventional spinal cord stimulator will have poor outcome eventually and these patients can be salvaged with converting the stimulator to high-frequency device. The high-frequency and low frequency waveforms can be combined in the same programme and this is only available with the NEVRO IPG.
		Expert 3: Yes also used at low frequency infrequently a. In my practice we have less than 1% using Senza at low frequency. Routine use is 10KHz b. Occasionally switched to low frequency if problems with 10k or loss of efficacy c. Senza is always programmed at 10KHz first. d. One or the other. As far as I am aware Senza is not able to offer different frequencies on the same lead.
5.	Related to the previous question, is Senza a first line option for SCS, or would it only be used after conventional low-frequency SCS has failed? a. If it may be used first line, as the EAG understands that low-frequency SCS requires paraesthesia mapping, would this be carried out when implanting Senza for high-frequency use, in case low-frequency was needed as an option in the future?	**Expert 1:** Senza would be inserted for patients with predominately back and leg pain as first line treatment. If a patient has had a previous trial of low frequency and failed depending on the individual case a senza HF10 trial may be offered a. No senza is anatomically placed and therefore parathesia mapping is not required
		Expert 2: It varies from centre to centre. Typically, in my centre, patients with combination of back and leg pain or neck pain and arm pain would receive a high-frequency spinal cord stimulator implant, whereas, most of the patients with typical neuropathic pain in the limbs would receive a conventional spinal cord stimulator. When using a high-frequency device we do not perform paraesthesia mapping on table.

#	Question	Answer
		Expert 3: Senza is a first line option for SCS. It is chosen by both patient and/or clinician choice. Senza is implanted anatomically; paraesthesia mapping is not needed but can be done. It is not needed even if low frequency is used in future.
6.	Approximately how many patients in the NHS receive treatment with Senza each year? And in which populations / subgroups?	**Expert 1:** I do not know these figures
		Expert 2: My guess would be that about 50-60% of all spinal cord stimulator implant in this country are NEVRO implants. They are typically used in patients with combination of back and leg pain or neck and arm pain.
		Expert 3: I don't know how many in the whole NHS (suggest asking NEVRO Corps). We do about 10-15 a year in Bristol. We use Senza (and all other SCS) for neuropathic pain in the limbs and low back pain. Newer indication is painful diabetic neuropathy.
7.	Are you aware of any changes in the use of Senza since NICE MTG41 was published in 2019? For example, changes to: a. Care pathways; b. Populations / subgroups in which its used; c. Uptake (is it now used more, or used less?).	**Expert 1:** This paper has influence trialling patient HF10 with diabetic neuropathy: JAMA Neurology 16/05/2022 Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy A Randomized Clinical Trial
		Expert 2: There have been no major changes since the guidance was published in 2019. There have been other newer spinal cord stimulator devices available and centres are using these to determine the real world outcome. However, more and more centres are now getting convinced that for patients with back and leg pain or neck and arm pain, high-frequency spinal cord stimulator is better than conventional or the newer SCF waveforms.
		Expert 3: a. no b. PSPS (persistent spinal pain syndrome) CRPS (complex regional pain syndrome), neuropathic pain in upper and lower limbs, low back pain c. increased awareness means increased uptake
8.	How do patients using Senza manage their treatment? Are they able to control their own "settings" and adjust as needed to control their pain, or is it done for them in clinic?	**Expert 1:** The device is programmed in clinic with potential of up to 5 programmes Patient have their own patient hand held controller and can adjust at home as per instructions.
		Expert 2: There are several parameter that can be adjusted by the patient but most parameters have to be programmed initially in the neuromodulation clinic. Patients will not have access to these parameters.

#	Question	Answer
		Expert 3: Both. Patients have a selection of settings and controls and ability to turn on and off. For more sophisticated updates or programming or major changes they will need to attend clinic.
9.	Are you aware of any adverse events or safety issues that may not have been found by the EAG in the literature, or by searching on the MHRA and FDA MAUDE websites?	**Expert 1:** Not aware of any adverse events
		Expert 2: No
		Expert 3: No

Appendix H – References

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