National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT330 Senza for delivering high frequency spinal cord stimulation to treat chronic neuropathic pain

Consultation comments table on first medical technologies consultation document

MTAC date: 16 February 2018

There were 137 consultation comments from 35 consultees (16 NHS healthcare professionals, 4 specialist societies, 5 manufacturers, 1 private sector and 9 patients). The comments are reproduced in full, arranged in the following groups according to the main issue raised in the relevant comment (**some comments contain multiple issues and have been split**):

- Clinical evidence (comments 1 to 51)
- Population (comments 52 to 60)
- Characteristics of the technology (comments 61 to 100)
- Comparator (comments 101 to 114)
- Benefits of the technology (comments 115 to 133)
- Patient choice and equality (comments 134 to 139)
- Cost model (comments 140 to 174)
- General (comments 175 to 180)

Clinical evidence: New evidence

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
1	6	NHS Professional	-	New Evidence relevant to the consultation not included in EAC report: The committee is advised to consult the below publications prior to reaching a final decision: a) De Andres et al (1) compared the Senza device to conventional stimulation in 60 patients with chronic, intractable pain of the trunk and/or limbs following surgery (FBSS) refractory to conservative therapy for at least 6 months with a pain score of 5/10 or more. The authors excluded patients with mechanical low back pain and tested for neuropathic pain in	Thank you for your comment. The External Assess Centre (EAC) reviewed the Thomson et al. (2017) study and considered it out of scope for this evaluation (see 2.1.2 of the EAC's advisory document for further details).

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				both groups at baseline and follow up. The authors were unable to blind the patients to the therapy but they blinded the observers. The authors found no significant difference between treatment with Senza or conventional stimulation on pain (NRS) disability (ODI), quality of life (SF12) , sleep (MOS-SS) or anxiety and depression (HAD) at 12 months or any other time point. We note that in contrast to the Senza study, de Andres et al conducted a single centre study, independent of industry and of higher quality design. The authors report no conflict of interest, devices were presented to patients as equally effective, assessors were blinded to the nature of the therapy and implantation procedures were standardised. Special attention was paid to standardising patient programming so that differences between programming personnel and their interactions with patients would not affect the results. We believe that this study, due to its single centre design, to be of a higher design quality and to have studied a more homogenous group of FBSS patients more likely to represent a neuropathic pain population as shown by the baseline Pain Detect scores of 18.87 and 16.23. Furthermore we believe that the impact of SCS on pain scores at 12 months to more closely align with our clinical experience than the results of the Senza study which UK clinicians have largely been unable to reproduce (2). We strongly believe the difference between the Senza and De Andres studies to be due to the different target populations, different sponsorship, particular attention to design issues peculiar to SCS studies exercised by De Andres et al and differences in healthcare settings between US private practice and public funded Spanish University hospital. b) Thomson et al (3) recently reported findings from the PROCO study at the 2017 Meeting of the International Neuromodulation Society . This UK multicenter double blinded randomised crossover trial of 20 patients with FBSS whose back pain is dominant over leg pain compared the clinical outcomes of patients implanted with commercially available SCS devices programmed in a random order to 10, 7, 4 and 1kHz current frequency following a washout period. No significant difference in clinical outcomes was found between any of the kHz frequencies. All patients experienced each kHz frequency for 4 weeks and chose their favourite kHz frequency for a further 3 months. 50% of subjects preferred 1kHz and the rest were distributed across the remaining kHz range. In all, each patient experienced kHz SCS for 9 months. This study due to its double blind design casts further doubt in our minds over the reported superiority of the higher frequency of 10Khz over other modes of stimulation.	The EAC considered the De Andres et al. (2017) study to be relevant new evidence for this evaluation. Details of the EAC's review can be found in sections 5 and 8 of the EAC's advisory document. In light of this new evidence, which conflicts with previously published evidence the EAC have revised their view on the evidence base and concluded that there is considerable uncertainty concerning the relative benefit of Senza HF10 compared with conventional low frequency SCS. The committee agreed with the EAC that the new evidence raised uncertainties about the benefit of Senza HF10 compared with low frequency SCS and the committee decided to change section 1.1 of the draft guidance.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				The above studies cast a troubling suspicion on the dominant clinical superiority of the Senza deice as reported by the manufacturer sponsored research (Kapural at al 2015,2016. Al Kaisy et al 2014 and Van Buyten et al 2013) . De Andres, J., et al. (2017). "Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome." Pain Med.doi 10.1093/pm/pnx241. 2. Thomson ST, et al . 29 May - 017. PATIENT RESPONSES TO PARESTHESIA-BASED SPINAL CORD STIMULATION AND KILOHERTZ FREQUENCY SPINAL CORD STIMULATION: Neuromodulation 2017;20:e336“e783.	
2	8	NHS Professional	-	The following relevant evidence (2 RCT's) have not been taken into account: 1. De Andres J, Monsalve-Dolz V, Fabregat-Cid G, Villanueva-Perez V, Harutyunyan A, Asensio-Samper JM, et al. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Med. 2017 Nov 04. PubMed PMID: 29126228. Epub 2017/11/11. 2.Thomson ST, M..Love-Jones, S. Patel,N. Jianwen W,,Que D, Moffitt, M. 29 May - 017. PATIENT RESPONSES TO PARESTHESIA-BASED SPINAL CORD STIMULATION AND KILOHERTZ FREQUENCY SPINAL CORD STIMULATION: in International Neuromodulation Societys 13th World Congress Neuromodulation: Technology Changing Lives Edinburgh, Scotland, United Kingdom (This is due to be published in January in the journal Neuromodulation) Both these RCTs, one a level one, multicentre, double blind RCT show that frequency of SCS is not necessary the only criteria in getting a good result and that 1KHz is as good as 10KHz (senza). There are also other companies that manufacture a 10KHz device.	Thank you for your comment. Please see the response to comment 1.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
3	15	Society	-	Has all of the relevant evidence been taken into account? The below two key papers in which randomised control trials (RCTs) were completed and have not been taken into consideration. De Andres et al, is a study done in Europe on the public sector compared to Senza done in the USA on the private sector. The study compared the Senza device to conventional stimulation in 60 patients with similar indication to the Senza RCT. They found no significant difference in various domains such as pain, disability, quality of life, sleep, anxiety and depression at 12 months. ' De Andres J, Monsalve-Dolz V, Fabregat-Cid G, Villanueva-Perez V, Harutyunyan A, Asensio-Samper JM, et al. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Med. 2017 Nov 04. PubMed PMID: 29126228. Epub 2017/11/11. Thompson et al, reported the PROCO study at the 2017 International Neuromodulation meeting. This is a UK multicentre double blinded randomised study on a similar patient group as the Senza RCT. Patients were implanted with a commercially available SCS device programmed in a random order 1,5, 7 and 10 kilohertz(Khz). The only criticism would be to say that the device used to deliver 10Khz was not the Senza system. All patients experienced each Khz frequency for 4 weeks and chose the frequency that they preferred for a further 3 months. If they couldn't choose as the effect was similar, the lowest frequency was chosen to reduce energy expenditure on the SCS device. 50% of the patients (10/20) preferred 1 Khz and the rest were distributed to other frequencies. This study shows that we still have no good data to determine if there are any other frequencies other than 10Khz which might achieve similar pain relief. ' Thomson ST, M..Love-Jones, S. Patel,N. Jianwen W,,Que D, Moffitt, M. 29 May - 017. PATIENT RESPONSES TO PARESTHESIA-BASED SPINAL CORD STIMULATION AND KILOHERTZ FREQUENCY SPINAL CORD STIMULATION: in International Neuromodulation Society's 13th World Congress Neuromodulation: Technology Changing Lives	Thank you for your comment. Please see the response to comment 1.

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				Edinburgh, Scotland, United Kingdom May 27“June 1, 2017. Neuromodulation. 2017;20:e336“e783.	
4	18	Manufacturer	-	The randomised trial by De Andres et al (Pain Medicine 2017; 0: 1“21 doi: 10.1093/pm/pnx241) concludes that the evolutionary pattern of the different parameters studied in our patients with FBSS does not differ according to their treatment by spinal stimulation, with conventional or high frequency, in one year follow-up. The study by De Andres et al showed no significant differences in pain, disability, anxiety or depression between randomised groups of High Frequency (HF10) or Conventional Frequency (10-40HZ) at any time point. The mean pain score measured by numeric rating scale improved from 7.69 before implant to 5.10 at 3 months for conventional spinal cord stimulation, and from 7.50 to 4.48 at 3 months for HF10. However, mean pain score subsided to 5.86 for conventional spinal cord stimulation and 6.06 for HF10 at 12 months. Similar results for HF10 compared to conventional spinal cord stimulation by 12 months were observed in disability, anxiety and depression scores. Van Buyten et al. (Neuromodulation 2017; 20: 642“649) conducted a retrospective review including 955 implants and 2,259 patient-years of follow-up from 3 European countries. They reported a rate of explants for inadequate pain relief of 5.0% per year for HF10 stimulation Vs 2.8% for non-rechargeable conventional systems. Perruchoud et al (Neuromodulation 2013; 16: 363“369) completed a randomized controlled double-blind placebo-controlled study based on the assumption that subthreshold HF SCS can produce analgesia without paraesthesia. Perruchoud et al state Under the condition of this trial, HFSCS was equivalent to sham for the primary outcome (improvement of PGIC) as well as for both the secondary outcomes (VAS and EQ-5D index). There was an obvious 'period effect• in the sense that effect of HFSCS and sham seems to be equal and only the order in the sequence, not the nature of the treatment, appears to dictate the effect. The four pieces of evidence that have been reviewed should cast some doubt on the reproducibility of findings from the Senza RCT in a real-world setting. Finally, the SCS system used as the control in the Senza study is a device that was introduced circa 2005. Today there has been significant changes to the SCS devices produced by all other SCS manufacturers	Thank you for your comment. Please see the responses to comments 1 and 143. The EAC considered the Van Buyten et al. (2017) study to be relevant new evidence for this evaluation. Details of the EAC’s review can be found in sections 3, 7 and 8 of the EAC’s advisory document. Please see the response to comment 143 for the impact of this study affects the economic analysis. Perruchoud et al (2013) was considered out of scope by the EAC because the study used a different device from another manufacturer, which utilised a different frequency, pulse width, and amplitude, compared with the Senza HF10 technology. Please see section 3.8 of the assessment report for further details. The EAC considered the Russo et al (2017) study to be out of scope because it used a different device from another manufacturer (see table 3 in section 2 of the EAC’s advisory document).

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				and some new entrants coming to market, also consider the compelling clinical results demonstrated in a recent article from Russo et al (industry sponsored) on a newer form of low frequency stimulation: Russo et al (Neuromodulation 2017; DOI:10.1111/ner.12684) recently published 6-month findings of conventional frequency stimulation (ï‚£60Hz). In this study the proportion of subjects with 50% relief was 92.6% (back pain) and 91.3% (leg pain) at three months, and 85.7% (back pain) and 82.6% (leg pain) at six months. The proportion with 80% pain relief was 70.4% (back pain) and 56.5% (leg pain) at three months, and 64.3% (back pain) and 60.9% (leg pain) at six months. Statistically significant improvements in mean BPI, EQ-5D-5L, ODI, and PSQI were also observed at both time points. Although only 6-month data the results are in line with the 6-month Senza data on both pain relief and quality of life measurements and supports the notion that newer forms of low frequency stimulation can also generate impressive outcomes in company sponsored clinical studies. **SEE APPENDIX 3 FOR REFERENCES**	
5	19	NHS Professional	1.1	New evidence is now available that casts doubt upon the association that high frequency SCS is associated with better pain control, improved quality of life, reduced functional disability than low frequency SCS.a) De Andres et al (1) compared the Senza device to conventional stimulation in 60 patients with chronic, intractable pain of the trunk and/or limbs following surgery (FBSS) refractory to conservative therapy for at least 6 months with a pain score of 5/10 or more. The authors excluded patients with mechanical low back pain and tested for neuropathic pain in both groups at baseline and follow up. The authors were unable to blind the patients to the therapy but they blinded the observers. The authors found no significant difference between treatment with Senza or conventional stimulation on pain (NRS) disability (ODI), quality of life (SF12) , sleep (MOS-SS) or anxiety and depression (HAD) at 12 months or any other time point. I note that in contrast to the Senza study, de Andres et al conducted a single centre study, independent of industry and of higher quality design. The authors report no conflict of interest, devices were presented to patients as equally effective, assessors were blinded to the nature of the therapy and implantation procedures were standardised. Special attention was paid to standardising patient programming so that differences between programming personnel and their interactions with	Thank you for your comment. Please see the response to comment 1. The Chella et al. (2015) study is a conference abstract. The EAC excluded all conference abstracts from the assessment report and the advisory document (please see section 2 for more details) because they did not provide sufficient detail to assess the study.

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				patients would not affect the results. We believe that this study, due to its single centre design, to be of a higher design quality and to have studied a more homogenous group of FBSS patients more likely to represent a neuropathic pain population as shown by the baseline Pain Detect scores of 18.87 and 16.23. Furthermore we believe that the impact of SCS on pain scores at 12 months to more closely align with our clinical experience than the results of the Senza study which UK clinicians have largely been unable to reproduce (2). We strongly believe the difference between the Senza and De Andres studies to be due to the different target populations, different sponsorship, particular attention to design issues peculiar to SCS studies exercised by De Andres et al and differences in healthcare settings between US private practice and public funded Spanish University hospital. b) Thomson et al (3) recently reported findings from the PROCO study at the 2017 Meeting of the International Neuromodulation Society . This UK multicenter double blinded randomised crossover trial of 20 patients with FBSS whose back pain is dominant over leg pain compared the clinical outcomes of patients implanted with commercially available SCS devices programmed in a random order to 10, 7, 4 and 1kHz current frequency following a washout period. No significant difference in clinical outcomes was found between any of the kHz frequencies. All patients experienced each kHz frequency for 4 weeks and chose their favourite kHz frequency for a further 3 months. 50% of subjects preferred 1kHz and the rest were distributed across the remaining kHz range. In all, each patient experienced kHz SCS for 9 months. This study due to its double blind design casts further doubt in our minds over the reported superiority of the higher frequency of 10Khz over other modes of stimulation. References 1. De Andres J, Monsalve-Dolz V, Fabregat-Cid G, Villanueva-Perez V, Harutyunyan A, Asensio-Samper JM, et al. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Med. 2017 Nov 04. PubMed PMID: 29126228. Epub 2017/11/11. 2. Chella Narendran RG, A. Eldabe,S. West, Garner,F & King,R. HF10TM spinal cord stimulation: Middlesbrough experience (181). Neuromodulation. 2015;18:e13“e106.	

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				3. Thomson S., Tavakkolizadeh M., Love-Jones S., Patel N, Gu W., Bains, A., Doan Q., Moffitt, M. Effects of Rate on Analgesia in Kilohertz Frequency	
6	19	NHS Professional	-	7. Conclusions - I think EAC and MTAC need to re-consider. - There are reasons to believe that the outcomes of both the investigator and comparator limbs of the Senza RCT are exaggerated due to a combination of lack of blinding, patient and observer bias, lack of equipoise. - Independent better quality RCT shows no difference in clinical outcomes of HF10kHz Nevro and parasthesia based SCS (1). - Other Independent Real world series fail to achieve as good results as Senza RCT. - A UK based multicentre trial shows no difference in clinical outcome between 1 and 10kHz SCS (3). References De Andres J, Monsalve-Dolz V, Fabregat-Cid G, Villanueva-Perez V, Harutyunyan A, Asensio-Samper JM, et al. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Med. 2017 Nov 04. PubMed PMID: 29126228. Epub 2017/11/11. Thomson S., Tavakkolizadeh M., Love-Jones S., Patel N, Gu W., Bains, A., Doan Q., Moffitt, M. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial " Neuromodulation 2018; 21.1: available on line ahead of print publication	Thank you for your comment. Please see the response to comment number 1.
7	20	Manufacturer	1.1	Quality of Evidence We are concerned by the statements that include 'the case for adopting Senza is supported by the evidence• (Section 1.1), 'there is strong evidence to support the claimed benefits• (Section 3.4), and the evidence is considered 'robust and adequate for decision making• (Section 4.1). We feel the statements fail to acknowledge the EACs comments about the	Thank you for your comment. Please see section 3.6.3 of the assessment report for the EAC's overall conclusions about the evidence.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				evidence in their assessment report. Considered together with the major limitations of the Kapural et al. trial, the results of available research do not support the conclusions in Section 1.1, 3.4, and 4.1 of the Medical Technology Consultation Document, namely that Senza high-frequency stimulation is superior to low-frequency stimulation and we would ask the committee to reconsider these conclusions. Most notably, these statements included in the consultation document are based primarily on the Senza clinical trial (Kapural et al., 2015) as noted by the EAC in Section 3.2. However, we believe it is important to emphasize that the conclusions drawn by the committee are not supported the EACs own assessment as well as a careful evaluation of the limitations of the Kapural et al. trial and of other available studies. 1. The most critical methodologic weakness of the Kapural et al. trial is the lack of investigator and patient masking, that is, the trial was an un-blinded open-label study that did not ensure clinical equipoise between both arms and, in which, both patients and study staff knew which treatments the patients received. 2. A recent review by Bicket et al., 2016 (Bicket, Dunn, & Ahmed, 2016) supports the conclusion that the Kapural et al. trial does not provide convincing evidence of the superiority of Senza high-frequency stimulation. In Table 1 of this article, ratings of 'poor• are given for bias in the Kapural et al. trial based on the fact that masking was not performed. Bicket et al. also describe that the Kapural et al. trial was an open-label design, which is completely consistent with this being a low-quality clinical trial. In contrast, Bicket et al. presents generally better bias ratings and provides a 'high quality• rating for a clinical trial by Perruchoud et al., 2013 (Perruchoud et al., 2013), which found no difference between high-frequency stimulation and a sham control in patients previously responsive to standard spinal cord stimulation. 3. In addition, the results of recent randomized trials by De Andres et al., 2017 (De Andres et al., 2017) and Thomson et al., 2017 (presented at the International Neuromodulation Society May 2017 and in press (Thomson, 2017), are also not consistent with the claimed superiority of high-frequency vs. low-frequency stimulation. Whilst we acknowledge that this evidence was not published during the initials stages of the Medical Technology Guidance process, we believe both studies are high quality	Please see the responses to comment numbers 1, 4 and 30. The Bicket et al. (2016) was identified during the EAC's initial systematic review and excluded because the systematic review included a device which was not Senza HF10. The two studies included in the review, the SENZA-RCT (Kapural 2015) and the study by Perruchoud (2012) are discussed separately in the assessment report.

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<tr><th>Comment no.</th><th>Consultee ID</th><th>Role</th><th>Section</th><th>Consultee comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>and clinically relevant and, as such, should be consider in your evaluation. Importantly, in contrast with the Kapural et al. trial, both of these trials were blinded. De Andres et al. note that 'The evaluators who collected pain ratings and other outcome measures were blinded to the subjects group allocations throughout the process• and patients were informed 'that there were two groups and that treatment was equally effective in both¦ (and) they might experience paresthesia as part of their treatment, but that this did not affect the final outcome of therapy.• Similarly, patients, treating and assessing physicians, and data collecting research nurses were blinded to the programmed therapy in the Thomson et al. trial. Both of these blinded trials found no significant differences between high- and low-frequency stimulation in patients with chronic low back pain.

SEE APPENDIX 1 FOR REFERENCES</td><td></td></tr>
<tr><td>8</td><td>20</td><td>Manufacturer</td><td>3.3</td><td>The other 5 studies were single-arm observational studies the results of which were generally supported and corroborated the results of Senza-RCT.

We are pleased to see that the draft guidance acknowledges the gaps in the evidence base for Senza. However, given that similar issues were raised about the five observational studies, we were disappointed to see that the EAC felt it appropriate to use them to corroborate the results of the Senza-RCT. We believe the EAC and the committee should consider additional observational studies (Table 3) as well as two recently published RCTs that do not corroborate the results of Senza-RCT, prior to issuing the final guidance.

Table 3

<table>
<tr><td>Type</td><td>Device</td><td>Author</td><td>Trial/Perm Design/ Numbers</td><td>Timeframe</td><td>VAS Delta</td><td>VAS Baseline</td><td>VAS End</td></tr>
<tr><td>Observational</td><td>Nevro Senza</td><td>Abejon (2014-NANS)</td><td>N/A n=18 (Back)</td><td>12 months</td><td>3.6</td><td>8.4</td><td>4.8</td></tr>
<tr><td>Observational</td><td>Nevro Senza</td><td>Eldabe et al. (2013-NANS)</td><td>78% n=36 (Back/Leg)</td><td>13 months</td><td>2.9</td><td>8.0</td><td>5.1</td></tr>
</table>
</td><td>Thank you for your comment. The studies identified were all conference abstract. The EAC excluded all conference abstracts from the assessment report and the advisory document (please see section 2 of the advisory document for more details) because they did not provide sufficient detail to assess the study.</td></tr>
</table>

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<tr><th>Comment no.</th><th>Consultee ID</th><th>Role</th><th>Section</th><th>Consultee comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Observational</td><td>Nevro Senza</td><td>Thomas (2013-NANS)</td><td>77% n=8 (Back/Leg)</td><td>3 months</td><td>1.6</td><td>6.4</td><td>4.8</td></tr>
<tr><td>Observational</td><td>Nevro Senza</td><td>Russo et al. (2013-NANS)</td><td>79% n=43 (Back)</td><td>9 months</td><td>4.0</td><td>8.0</td><td>4.0</td></tr>
<tr><td>Observational</td><td>Nevro Senza</td><td>Russo et al. (2013-INS)</td><td>78% n=54 (Back)</td><td>9 months</td><td>4.0</td><td>7.0</td><td>3.0</td></tr>
<tr><td>Observational</td><td>Nevro Senza</td><td>Brouns et al. (2016-WIP)</td><td>N/A n=22 (Back)</td><td>Not reported (NR)</td><td>NR</td><td>NR</td><td>NR</td></tr>
</table>

Senza observational studies show a 50% average pain relief. This is no different from the most recent low frequency technology observational study recently published in Pain Medicine 2017 (Veizi et al., 2017), which showed 57-59% pain relief at 2-years. In addition, Pain Medicine just published a European RCT (De Andres et al., 2017) comparing Nevro 10 kHz to standard rate SCS. The study concluded that pain and functional outcomes out to 1 year were the same for HF10 and standard rate. Finally, in the UK, the PROCO RCT (Thomson, 2017) compared 1 kHz, 4 kHz, 7 kHz, and 10 kHz using a robust double blind crossover design. The PROCO RCT concluded that there was no difference in pain or functional outcomes between frequencies.

SEE APPENDIX 1 FOR REFERENCES
</td><td></td></tr>
<tr><td>9</td><td>23</td><td>NHS Professional</td><td>3.1</td><td>PROCO study should also be considered which shows a different outcome.</td><td>Thank you for your comment. Please see the response to comment number 1.</td></tr>
<tr><td>10</td><td>27</td><td>NHS Professional</td><td>-</td><td>Our experience of doing HF10 Spinal cord stimulation for treating chronic neuropathic pain at Lancashire Teaching Hospitals NHS foundation Trust

- 1.5 million catchment area

- Around 35 SCS implants per year

- Introduced HF-10 in 2013 for failed low frequency trial patients or patients with predominant back pain

- Due to encouraging results the scope for HF-10 gradually evolved to encompass mixed back and leg pain patients</td><td>Thank you for your comment. The committee welcome comments on experience with the technology in the NHS.</td></tr>
</table>

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				Preston have 72 implanted patients ranging from 3 months to 4 years - soon to be 74 " today! * Average leg pain relief across 48 months is 63% * Average back pain relief across 48 months is 60% * Over 80% of 72 patients are responders (achieving 50% pain relief or more) out to 48 months. * Zero explants, pocket pain or complaints of paresthesia * 1/72 x Infection at the anchor site. * 3/72 x Lead Migrations * Trial conversion rate runs at 91%	
11	27	NHS Professional	-	we presented a poster at the EFIC (copenhagen 2017) on HIGH FREQUENCY SPINAL CORD STIMULATION (HF-SCS) AT 10 KHZ RESULTS IN SUSTAINED PAIN RELIEF AND IMPROVED FUNCTIONAL OUTCOMES	Thank you for your comment. The study identified was a conference abstract. The EAC excluded all conference abstracts from the assessment report and the advisory document (please see section 2 for more details) because they did not provide sufficient detail to assess the study.
12	28	Society	-	The committee should be aware of two recently published pieces of evidence: 1) the randomised trial of Senza versus standard SCS reported by De Andres et al (Pain Medicine 2017 Nov 4. doi: 10.1093/pm/pnx241). This should be included as we believe it satisifes the criteria set out in the assessment report. This showed no difference in outcomes between the two types of system. This is the second major RCT of Senza (after the Nevro-sponsored trial itself), but with very different results, and calls into question the conclusions drawn in the draft document about relative efficacies. In turn we expect this will have a significant impact on the economic assessment.	Thank you for your comment. Please see the response to comment number 1.

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				2) The PROCO randomised controlled trial (NCT02549183) " a three centre UK study comparing stimulus frequencies in the range from 1kHz to 10kHz. The results of this were presented at the NSUKI Annual Scientific Meeting in Oxford in November 2017 and are due to be published in 2018. There was no significant difference in efficacy at any of the different stimulation frequencies; in particular 10kHz (as used in Senza) was not more effective than much lower frequencies. (Thomson S., Tavakkolizadeh M., Love-Jones S., Patel N, Gu W., Bains, A., Doan Q., Moffitt, M. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial " Neuromodulation 2018; 21.1:)	
13	29	Manufacturer	1.1	Reliability of section 1.1 and relevant evidence. We note that recent evidence contradicts section 1.1, making this section unreliable. The randomised trial by De Andres et al (Pain Medicine 2017; 0: 1"21 doi: 10.1093/pm/pnx241) concludes that the evolutionary pattern of the different parameters studied in our patients with FBSS does not differ according to their treatment by spinal stimulation, with conventional or high frequency, in one year follow-up. It is important that all the available evidence is taken into account. The trial by De Andres et al not only contradicts point 1.1, but also casts doubt over that claim that Senza HF10 offers clinically superior pain relief for most people with back or leg pain compared with low frequency spinal cord stimulation.	Thank you for your comment. Please see the response to comment number 1.
14	29	Manufacturer	1.1	Reliability of section 1.1 and relevant evidence. Since Senza-RCT, there have been several recent publications comparing outcomes of HF10 and conventional spinal cord stimulation that should be considered and give real-world experience with which to compare the Senza RCT. Van Buyten et al. (Neuromodulation 2017) conducted the largest known study of real-world spinal cord stimulation outcomes, a retrospective chart review including 955 implants and 2,259 patient-years of follow-up. They reported a rate of explants for inadequate pain relief of 6.9% for non-rechargeable spinal cord stimulation, 11.2% for conventional rechargeable spinal cord stimulation and 14.2% for HF10 stimulation. The increased explant rate for HF10 was not found to be statistically significant in multivariable regression, but the real-world findings diverged markedly from expectations for HF10 set by the Senza RCT. Specifically, SENZA RCT showed almost no loss of efficacy at 24 months, compared with Van Buytens data that showed 14.2% of devices explanted at a median of 2.2 years for inadequate pain relief (lack of efficacy).	Thank you for your comment. Please see the responses to comment numbers 4 and 143.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
15	29	Manufacturer	2.4	Claim: Increased achievement of a successful outcome (greater than or equal to a 50% reduction in pain) compared with low frequency SCS. A multicentre, double-blind crossover RCT by Thomson and colleagues from the United Kingdom found no difference in patient-reported pain scores or quality-of-life measurements for 1 kHz vs. 10 kHz (HF10) stimulation. Importantly, conventional spinal cord stimulators currently on the market are capable of delivering 1 kHz frequency stimulation. Findings from the study were presented at the International Neuromodulation Society in Edinburgh in May 2017, although it has not yet moved into full publication. However, the Institute should consider this and be mindful of issuing guidance that could be contradicted by UK evidence and render this claim at best, disputed.	Thank you for your comment. Please see the response to comment number 1.
16	29	Manufacturer	2.4	Claim: A significantly better functional outcome. The publication by De Andres et al shows no difference in disability scores between conventional spinal cord stimulation and HF10. A series of publications from Kinfe, Mohammed et al. (Neuromodulation 2016 and 2017) report on a study of 16 patients with alternating implants of HF10 or BurstDR stimulation to facilitate a head to head comparison of the two modalities. This pilot study found long-term back pain reduction of 87.5% for Burst stimulation, compared to reduction of 54.9% for HF10, but the difference was not significant. Leg pain was reduced an average of 50.2% for Burst but increased 18.0% for those receiving HF10, and the reduction for Burst was statistically significant. Finally, there were no significant differences between groups in functional outcomes, including sleep quality and depression. The claim of significantly better functional outcome is therefore disputed in the literature and thus should not be upheld.	Thank you for your comment. Please see the response to comment number 1. Publications from Kinfe et al. (2016) and Mohammed et al. (2017) were excluded by the EAC as they were out of scope. Please see section 3.3 of the assessment report for further details.
17	31	NHS Professional	-	As far as long term studies we have seen a number of patients over 5 years who continue to use the device and we recently published data on 3 year outcomes on a group of patients with pain who did not have previous surgery: Adnan Al-Kaisy, Stefano Palmisani, Thomas E. Smith, Roy Carganillo, Russell Houghton, David Pang, William Burgoyne, Khai Lam, Jonathan Lucas; Long-Term Improvements in Chronic Axial Low Back Pain Patients Without Previous Spinal Surgery: A Cohort Analysis of 10-kHz High-Frequency Spinal Cord Stimulation over 36‰Months, Pain Medicine, , pnx237, https://doi.org/10.1093/pm/pnx237 https://academic.oup.com/painmedicine/advance-article/doi/10.1093/pm/pnx237/4564171	The EAC deemed the Al-Kaisy et al. (2017) study to be relevant new evidence for this evaluation. Details of the EAC's review can be found in sections 4 and 8 of the EAC's advisory document. On consideration of this new evidence the committee decided that although it was supportive of the draft recommendations alternative new evidence has resulted in uncertainty of the evidence base therefore the committee decided to change section 1.1, 3 and 4 to reflect this uncertainty

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
18	32	Society	-	The British Pain Society is aware of two further studies (De Andres J et al. and Thomson ST et al.) that have since been published which do not show any added advantage for SENZA over other stimulation frequencies.	Thank you for your comment. Please see the response to comment number 1.
19	33	NHS Professional	-	I have been practicing Neuromodulation for the last 20 years. One of the advances of implant technology which had great impact in my practice (other neuromodulators throughout the world) is 10 kHz High-Frequency Spinal Cord Stimulation (HF10) .We were privileged to take part in the first open label study of this therapy back in 2009 (1). Ever since HF10 SCS has become standard practice in the management of back and leg pain in our centre. We also demonstrated in an open label study that HF10 has a role in the management of patients who are suffering from chronic lower back pain whom are not suitable for spine surgery (1,2). In a most recent study in our centre we have demonstrated that the higher frequency is better outcome compare to the baseline measurment. The SCS Frequency Study is a prospective, randomized, double-blinded, sham-controlled, cross-over study designed to evaluate the safety and efficacy of SCS using sub-perceptual threshold amplitude levels at 4 different frequencies and pulse widths settings (sham stimulation, 1200Hz@180Î¼s, 3030Hz@60Î¼s, and 5882Hz@30Î¼s) in individuals diagnosed with FBSS who respond to conventional stimulation settings during a SCS trial. Here we report efficacy data from the double-blinded, sham-control, 12-week cross-over phase of the SCS Frequency Study (3). Giving the fact that there is type 1 evidence RCT, other open label studies and accumulative clinical experience for the last eight years in using HF10 SCS for back and leg pain. I would highly recommend this therapy to be approved by NICE for back and leg pain. References: 1. Al-Kaisy A, Palmisani S, Smith TE, Pang D, Lam K, Burgoyne W, Houghton R, Hudson E, Lucas J. 10 kHz High-Frequency Spinal Cord Stimulation for Chronic Axial Low Back Pain in Patients With No History of Spinal Surgery: A Preliminary, Prospective, Open Label and Proof-of-Concept Study. Neuromodulation: Technology at the Neural Interface. 2017;20:63“70. 2. Adnan Al-Kaisy, Stefano Palmisani, Thomas E. Smith, Roy Carganillo,	Thank your comment. Please see the response to comment number 17. The EAC has reviewed the Al-Kaisy et al. (2018) study and consider it to be out of scope as not Senza device not used (see section 2 of the EAC’s advisory document for further details).

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Russell Houghton, David Pang, William Burgoyne, Khai Lam, Jonathan Lucas; Long-Term Improvements in Chronic Axial Low Back Pain Patients Without Previous Spinal Surgery: A Cohort Analysis of 10-kHz High-Frequency Spinal Cord Stimulation over 36‰Months, Pain Medicine, , pnx237, https://doi.org/10.1093/pm/pnx237 https://academic.oup.com/painmedicine/advance-article/doi/10.1093/pm/pnx237/4564171 3. Al-Kaisy A, Palmisani S, Sanderson K, Tan Y, McCammon S. A randomized, sham-control, double blind, cross-over trial of sub-threshold spinal cord stimulation at various kilohertz frequencies (SCS Frequency Study). North American Neuromodulation Society Meeting, Las Vegas, US. December 2015. (In Press) Neuromodulation Journal.	
20	35	Manufacturer	-	HF10, as currently marketed, is only one of several options that can be tailored to achieve optimal clinical outcomes for patients in this complex area. We believe that a single randomised controlled trial (RCT), (1) with a high risk of performance and detection bias, as highlighted in the EAC assessment report, is insufficient for the EAC to conclude that "there is good evidence that HF10 that Senza HF10 improves clinical outcomes compared with traditional low frequency SCS and that this generalises to NHS patients". (assessment report page 5) [redacted] are aware that the EAC is one of many sources of evidence the committee review in arriving at their decision and we therefore ask that committee is made aware of the following RCTs. New evidence in the form of two Randomised Controlled Trials (2,3) and an International Retrospective Chart Review Study (4) have been reported since the EAC concluded their evidence review for this draft guidance. The findings of the Senza RCT have not been replicated in these new studies, which report significantly different results in terms of efficacy, complication and explant rates, which are key drivers of the economic model. This raises a considerable question about the replicability and generalisability of this single RCT comparing HF10 therapy to conventional SCS. These new, high quality studies shed valuable clinical evidence and	Thank you for your comment. Please see the response to comments number 1, 4 and 30.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				warrant consideration in the evidence review process for this guidance. The new evidence presents a challenge to the conclusion of the EAC that "the results from the SENZA-RCT, supported by data from the single-armed studies, provided unequivocal evidence that the use of Senza HF10 therapy is associated with a large and sustained reduction in back and leg pain in the indicated population". (assessment report page 42) We strongly urge the Committee to revert the submission back to the evidence assessment stage of the process, to enable the EAC to incorporate this new evidence into their assessment and we request that results from these new publications relating to trial success, optimal pain relief, complication rates and explant rates are tested in the model. This will ensure that any NICE guidance issued will be based on the full body of currently available evidence. We believe there are several relevant points for the EAC to reconsider: • The claims and evidence for HF10 • The assumptions used in the economic modelling. • The definition of the Senza device and HF10 therapy as a distinct and separate therapy to conventional spinal cord stimulation (SCS), **SEE APPENDIX 2 FOR REFERENCES**	
21	35	Manufacturer	-	Claims and evidence for HF10 - Evaluation of relevant evidence An independent (non-industry sponsored) prospective, blinded RCT comparing HF10 to conventional SCS was conducted by De Andres et al (2017). (2) The study design improved on the Senza RCT by concealing randomization assignment from the evaluator who collected the outcome measures. In addition, the implanting physician did not participate in further assessments, to limit potential bias. Patients were informed that there were two groups and treatments were equally effective. The trial was designed to show superiority of HF10 over conventional SCS, but did not yield significant differences in pain, disability, anxiety or depression between groups at any time point. At 12-months, mean pain scores measured by NRS were similar, 5.86 for conventional SCS and 6.06 for HF10. Similar trends towards a levelling of effectiveness for HF10 compared to conventional SCS by 12 months were observed in disability, anxiety and depression scores. This well-designed RCT fails to replicate	Thank you for your comment. Please see the response to comment number 1.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				the results of Senza RCT. A UK, multicentre, double-blind crossover RCT by Thomson et al (3) found no difference in patient-reported pain scores or quality-of-life measurements for 1 kHz, 4 kHz, 7 kHz and 10 kHz (HF10) stimulation. All frequencies, including 10kHz, provided equivalent improvement in pain. Currently available conventional SCS systems can deliver 1 kHz frequency stimulation. These two new RCTs (2,3) and other post-market studies have failed to demonstrate the superiority of HF10 to conventional SCS. In addition, they fail to replicate the level of pain relief observed in the Senza RCT. The largest report of HF10 was published by Russo et al (2016) (5) in a retrospective, multicentre review of 256 patients receiving HF10. In this real-world setting, they reported a 73% trial to implant rate and a mean 50% reduction in pain scores at 3 and 6 months post-implant. This is a lower success rate than seen in the Senza-RCT, both in trial-to-implant rate (92.8%) and average percent reduction in pain. **SEE APPENDIX 2 FOR REFERENCES**	
22	29	Manufacturer	2.4	Claim: Clinically superior pain relief for most people with back or leg pain. The trial by De Andres et al noted against section 1.1 contradicts this claim. Specifically, the trial by De Andres et al was designed to show superiority of HF10 over conventional spinal cord stimulation but did not yield significant differences in pain, disability, anxiety or depression between groups at any time point. Mean pain score measured by numeric rating scale improved from 7.69 before implant to 5.10 at 3 months for conventional spinal cord stimulation, and from 7.50 to 4.48 at 3 months for HF10. However, mean pain score subsided to 5.86 for conventional spinal cord stimulation and 6.06 for HF10 at 12 months. Similar trends towards lesser numerical effectiveness for HF10 compared to conventional spinal cord stimulation by 12 months were observed in disability, anxiety and depression scores. Other published and presented data from Russo, Kinfe, Muhammed, Thomson and Slotty also are non-corroborative of the SENZA RCT data. Additional evidence means that the claim of clinically superior pain relief for most people with back or leg pain cannot be reliably upheld in routine practice.	Thank you for your comment. Please see the response to comment numbers 1, 4 and 16. Slotty et al. (2014) was excluded by the EAC at the assessment report stage as Senza was not used.
23	34	NHS Professional	-	I have implanted 74 patients over a 4 year period and have presented my results most recently at NSUKI 2017. We have comparable results to the Senza RCT in back and leg pain patients averaging 61% pain relief out to	Thank you for your comment. . The committee welcomes comments on

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				4 years in some cases. My permanent explant rate is 0/74. There has been 1 infection requiring revision and re-implantation. In summary the system seems very efficacious and safe.	experience with the technology in the NHS.
24	18	Manufacturer	-	In addition, there are other research published or soon to be published by different groups (not company sponsored) that contradict findings from the Senza study. The recently presented (awaiting publication) double blind randomised controlled study, PROCO by Thomson et al (2) investigated the effectiveness of (sensation free) stimulation delivered between 1 and 10 KHz. The study involved 20 patients and was statistically powered based upon the number of stimulation separate frequencies used to stimulate the patients. This study reports no statistical significant difference between the varying frequencies, in fact 1KHz was deemed to deliver the best pain relief by the patients. Secondary endpoints of quality-of-life measurements also showed that there was again no statistical difference between frequencies ($p>0.8$). This is consistent with preclinical studies from Shechter et al (2013) as well as Song et al (2014) who found no difference in effect between different frequencies of stimulation in a rat model of neuropathic pain. **SEE APPENDIX 3 FOR REFERENCES**	Thank you for your comment. Please see the response to comment number 1.
25	5	NHS professional	-	Since NICE commissioned this review there have been other publications that have showed 1kHz frequency produces similar results as 10kHz Senza systems. A very well designed trial by De Andres et al compared the Senza device to conventional stimulation in patients with chronic, intractable pain of the trunk and/or limbs following surgery. They found no significant difference between treatment with Senza or conventional stimulation on pain scores, disability, quality of life, sleep or mood at 12 months or any other time point.	Thank you for your comment. Please see the response to comment number 1.

Clinical evidence: Therapy success

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
26	4	NHS Professional	-	True evaluation of therapy success with HF10 (and low frequency SCS), should be measured by improvement in functional ability, based on patient- set goals, rather than purely on a 50% reduction in VAS score.	Thank you for your comment. Please see the responses to comment numbers 53 and 180.
27	5	NHS Professional	-	All the studies published so far for HF10 therapy were commissioned by NEVRO, the manufacturer including the Australian Real life case series. These all produced spectacular results that were mirrored among all the publications across all the continents. I have been using this technology for almost 7 years since its CE marking in 2010. I have not seen or heard any centre using Senza in the UK having similar results as published in HF10 studies. Rather our results match what is published in older spinal cord stimulation studies. We would get 50% improvement in pain scores and 40-50-% improvement in quality of life and function.	Thank you for your comment. In this evaluation the EAC identified and reviewed all the relevant evidence associated with Senza. Please see the responses to comment numbers 1, 4, 17 and 143. The study by Rapcan et al. (2015), included in the EAC's assessment report, does not report any declaration of interest for any manufacturer.
28	6	Society	-	The Senza study was conducted exclusively in US private practice centres. It is unclear to us how the trial intervention or control devices were funded or whether the recruited subjects would have accessed these devices out with the study. The mechanism of funding of the study devices is relevant since it may have contributed to the extraordinary result of the study. We believe that this may impact the generalisability of the study results into the NHS. It is, for example, our experience as supported by literature (1) that few patients report 50% back pain relief with a conventional SCS at 24 months. In contrast 50% of the Senza study control arm report 50% pain relief at 24 months using conventional stimulation. This unusual result in the control arm is contrary to our experience and most of the conventional SCS literature on back pain. 1. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain. 2007 Nov;132(1-2):179-88	Thank you for your comment. Please see the responses to comment 1 and 27. The Kumar et al. (2007) study was judged by the EAC to be out of scope as the Senza device was not used. The EAC identified the funding of the SENZA-RCT was provided by Nevro corp and reported this as a risk of bias. The EAC reviewed the Financial Disclosure in the FDA Summary of Safety and Effectiveness Data (SSED) for Senza (May 2015) stated, "the applicant had adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
					information provided does not raise any questions about the reliability of the data." The EAC consider this provides external and independent assurance from the FDA that the Senza RCT data was not considered biased by any financial interests conflicts of interest.
29	5	NHS professional	-	It is my opinion that whilst Senza HF10 has some specific advantages and has enabled me to improve pain relief in some of patients who could not have benefited in the past with SCS therapy, in real life it doesn't produce the same spectacular results as published in the clinical trials. It could not be one therapy that fits / treats all the pain patients.	Thank you for your comment. Please see the responses to comments 1 and 134.

Clinical evidence: Study quality

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
30	19	NHS Professional	-	7. Conclusions - I think EAC and MTAC need to re-consider. - There are reasons to believe that the outcomes of both the investigator and comparator limbs of the Senza RCT are exaggerated due to a combination of lack of blinding, patient and observer bias, lack of equipoise.	Thank you for your comment. Please see response to comment 1. The EAC reported on these sources of potential bias in the assessment report. They are further discussed in Section 5.5 of the advisory document.
31	5	NHS Professional	-	It is my opinion that superior results produced in HF10 (Senza) studies could be due to observer bias during data collection, altered patients expectations due to the wordings of patient information during consent process, patients thinking that they are getting new innovative superior therapy etc. We do not have information on how many programming sessions of what duration and how many follow up appointments the patients in the study had. This could tip the balance in favour of technology being assessed. Indeed the results in comparator arm of Senza study that used paaresthesia based stimulation produced far superior pain relief with traditional paraesthesia based stimulation from axial back pain than what we see in real life.	Thank you for your comment. Please see the response to comment number 30.
32	5	NHS Professional	-	With Senza technology that is paraesthesia free one could have done double blind, randomised sham controlled study; however this has never been done. It is possible to program the devices so that the battery runs	Thank you for your comment. Please see the response to comment number 30.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				down at the same rate and takes similar time to recharge in a sham group of patients. In spite of this no sham controlled study was commissioned. NEVRO has never been able to explain this satisfactorily.	
33	2	Patient	-	Concern about conflicts of interest here. What materials were patients exposed to ? biased US website indicating that this device was "new", "better" can have a significant influence on pain and placebo.	Thank you for your comment. Please see the responses to comment numbers 30 and 37.
34	6	NHS Professional	-	We note the EAC comment on the potential for bias in the Senza study, chief among the sources of bias being the lack of blinding of the subjects . We would like to draw the committee's attention to the study by Perruchoud et al (1) where 36 subjects implanted with SCS and suffering with neuropathic pain were randomized to either High Frequency at 5 KHz or sham stimulation in. No significant difference was found between the High Frequency group and the sham group on either global perceived effect, pain, or quality of life. In this study blinding was maintained and checked at crossover points. We would also like to point to the committee to a number of sources of bias common in neuromodulation studies that have not been highlighted by the EAC analysis: 1. Patient expectations: a number of pain studies (2-3)have shown that patient expectations play a strong role in determining outcomes of pain therapies. It is therefore reasonable to assume that in a study comparing old to new technology, patients randomized to the novel therapy will have higher expectations thereby influencing their outcomes. The reverse will be the case for a group randomized to traditional therapy. 2. Observer bias is a well-studied (4-5) phenomenon. We note that the observers could have been blinded in the Senza study but were not. In contrast De Andres et al blinded the observers to the nature of therapy. 3. Programmer bias: based on our clinical experience of conducting industry sponsored neuromodulation trials, we observed that the person or persons programming the neuromodulation device can exert an influence on the participant's reported outcomes. Of note, in novel device studies, it is usually the sponsor's representatives who program the new technology. This introduces a further risk of bias against existing devices that are usually programmed by medical centre staff.	Thank you for your comment. Please see the response to comment numbers 4 and 30.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				4. Number of programming contacts: Number of study related visits has also been demonstrated to exert a strong influence on pain reported outcomes (6). The Senza study authors do not report the number of face to face programming sessions in either arms neither do they report any telephone contact that are well known to occur follow a programming session from an industry representative to participants. 5. Finally the impact of industry sponsorship needs to be taken into account; a recent paper entitled 'Head-to-head randomized trials are mostly industry sponsored and almost always favour the industry sponsor'(7) finds that such studies report a result in favour of the sponsor in 96.5% of 57 industry sponsored trials. 1. Perruchoud C, Eldabe S, et al. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. Neuromodulation. 2013 Jul;16(4):363-9 2. Linde K, et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. Pain. 2007 Apr;128(3):264-71 3. Cormier S, et al. Expectations predict chronic pain treatment outcomes. Pain. 2016 Feb;157(2):329-38 4. Hrobjartsson A, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. BMJ. 2012 Feb 27;344 5. Hrobjartsson A, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. CMAJ. 2013 Mar 05;185(4). 6.Vase L et al. Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: A meta-analysis of the individual data from nine industrially sponsored trials. Pain. 2015 May 4;156(9). 7.. Flacco ME, et al. Head-to-head randomized trials are mostly industry	

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				sponsored and almost always favor the industry sponsor. J Clin Epidemiol. 2015 2015 Jul;68(7):811-20	
35	18	Manufacturer	-	Comments on NICE Medical Technology Consultation Document: Senza for Delivering High Frequency Spinal Cord Stimulation to Treat Chronic Neuropathic Pain It would appear that the major claim in this technology consultation is that the Nevro Senza SCS System is clinically superior to other SCS systems and that this clinical superiority is achieved by setting the stimulation output to 10Khz. This proposition is based on the results from a single, company sponsored, RCT in which the Senza system was compared to one other, particular SCS system. Additionally, the question is posed as to whether being able to drive/sleep with the device on and not using patient feedback during the lead implant procedure adds significant quality of life improvement or brings cost savings. This is rather shaky ground on which to be making such a proposition. The RCT in question had significant sources of bias; it was not blinded and company employed representatives had regular contact with the patients in the study to program/reprogram the device. Only the lack of blinding is discussed in the published article, representative contact was not controlled, nor is the fact that patients enrolled in this study were well aware if they are being treated with the new device or the old device which adds further bias to the lack of blinding. Additionally, the study in question is designed to achieve an FDA approval for the commercial release of the system in the US. The US accounts for 75% of the global SCS market and as such, running a successful trial (from the sponsors point of view) is a make or break objective of the sponsoring company. It is commonly accepted that most Industry sponsored studies produce results that are favourable to the sponsor in the medical device industry. According to M.E. Flacco et al (Journal of Clinical Epidemiology 68 (2015) 811-820) Industry-sponsored comparative assessments systematically yield favourable results for the sponsors, even more so when non-inferiority designs are involved. **SEE APPENDIX 3 FOR REFERENCES**	Thank you for your comment. Please see the responses to comments 1, 30 and 90.
36	19	NHS Professional	3.4	"The EAC concluded that there is strong evidence to support the claimed benefits presented by the company in the case for adoption. However, it noted gaps in the evidence base, particularly the lack of long-term	Thank you for your comment. Please see the response to comment number 7.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				studies." Given the concerns already mentioned I cannot see how the EAC can consider the evidence from a non-blinded, open label and subject to important patient and investigator bias to be considered "strong". Either it is inconclusive or at the very best it is of such low quality that it is insufficient to recommend superiority.	
37	20	Manufacturer	3.2	Although it identified the potential for performance, detection and reporting bias, the EAC was satisfied that the trials limitations did not affect the overall direction of the results. We are disappointed that the consultation appears to undervalue the concerns about the Senza RCT highlighted by the EAC in their assessment report (page 30). In particular, we feel that the EAC did not fully evaluate or explain the impact that the performance, detection and reporting bias had on the results of the Senza-RCT. In the External Assessment Centre Report (page 30), the EACs own critical appraisal of the Senza-RCT noted that due to the open-label and un-blinded structure of the study 'meant there was a high risk of performance and detection bias.• Discounting the statement above falls below the high standard NICE usually applies. Kapural et al. discuss several limitations of their trial, specifically, effects of pain medication, the lack of masking (i.e., blinding), differences between devices in charging protocols, definition of pain remission, and diagnostic heterogeneity. The most critical of these is the lack of investigator and patient masking, that is, the trial was an un-blinded open-label study in which both patients and study staff knew which treatments the patients received. In view of this research design, it must be emphasized that a large number of studies of various types of pain have provided compelling evidence that the expectations of patients and clinicians can have a very substantial impact on patient outcomes (Colagiuri, 2010; Enck et al., 2013; Tracey, 2010). Because the investigators and patients in the Kapural et al. trial were not blinded, we believe the committee and the EAC should have evaluated the possibility that the results of the study could have been explained by patient expectations and/or by the expectations of investigators and other study staff being communicated to patients. Furthermore, we feel it is regrettable that a review of the printed and other	Thank you for your comment. Please see the responses to comments 1 and 30. The EAC deemed a review of "printed and other material (e.g., websites) for the Senza-RCT patient recruitment phase" is beyond the scope of critical appraisal. The EAC has identified sources of bias, but it is not possible to quantify the effect of bias on reported results, other than speculatively.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				material (e.g., websites) for the Senza-RCT patient recruitment phase was not conducted. A large number of studies have demonstrated that positive and negative expectations can have a substantial impact on symptoms such as pain, depression, sleep, and physical function (Kam-Hansen et al., 2014; Rutherford & Roose, 2013; Schedlowski, Enck, Rief, & Bingel, 2015; Weimer, Colloca, & Enck, 2015). We believe Nevros study recruitment brochure made available to SENZA study participants had the potential for creating positive expectations for Nevros 10 kHz therapy in the test arm and negative expectations towards traditional SCS in the control arm. For example, Nevros study the brochure states 'the Senzaâ„¢ system is designed to treat chronic pain in the trunk and/or limbs at least as effectively and without some of the potential side effects associated with currently available SCS systems.• Nevros website further suggested that high-frequency is preferred over low-frequency by stating, 'only the Nevro System delivers the unique waveforms designed to offer compelling back pain relief and avoid the side effects commonly associated with conventional SCS. In addition to the beneficial effects of positive expectations, we would ask the committee to also recognize that nocebo effects, as a result of adverse expectations, are common, and can contribute to a lack of improvement " for example, in the control arm of a clinical trial " when patients believe they have received an ineffective or inferior treatment (Rief et al., 2011; Vase et al., 2015a). The nocebo effect is clearly evident in both the brochure and on the recruitment website, particularly as it pertains to the description of paresthesia. For example, the study recruitment brochure states 'The Senza system is designed to treat chronic pain in the trunk or limbs without the need for a buzzing sensation. In addition, the patient website included negative statements about paresthesia, including the following quotes: 'The goal is to provide superior efficacy without the uncomfortable stimulations commonly experienced with SCS therapy.; 'Designed to deliver relief without paresthesia or uncomfortable stimulation• and 'Additionally, conventional SCS is accompanies by paresthesia, which helps to 'mask• the pain but can cause discomfort such as tingling and uncomfortable stimulation.• Given the EACs assessment for the high risk of performance, detection and reporting bias in the Senza-RCT and the biased language evident in Senzas recruitment materials, we believe it is impossible to reach the	

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				EACs final conclusion that trials limitations did not impact the overall direction of the results. **SEE APPENDIX 1 FOR REFERENCES**	
38	20	Manufacturer	4.1	the evidence supporting the clinical benefits of Senza compared with low frequency SCS was robust and adequate for decision-making We are concerned about the evidence used during this evaluation and would ask that you note our disappointment that the evidence submitted by the applicant is very limited and a departure from the level of evidence submitted for other Medical Technology Guidance applications reviewed by NICE. The evidence consists of a single, industry-funded RCT and a few observational studies with no comparison cohorts. We feel it is particularly regrettable that the evidence submitted did not contain an independent study supporting the superiority of HF10, yet the applicant claims superiority on a subjective, patient-reported outcome (VAS score). Furthermore, we do not agree that the statement that 'the consistency of the study results available were sufficiently convincing to conclude that the evidence supported claimed patient benefits• can be made given the questions raised by the EAC about the quality of the publications considered. We would like to suggest that this sentence is removed.	Thank you for your comment. Please see the responses to comments 7 and 27.
39	32	Society	-	Thank you for giving us the opportunity to comment on the MTEP on Senza. The British Pain Society welcomes the support of NICE in the use of latest technology and evidence for improving patient care by alleviating pain and other distressing symptoms. The Council and the wider membership of the society have discussed the MTEP and a summary of the comments is given below for consideration. The document gives the impression that SENZA is better than all other forms of spinal cord stimulation and this is not consistent with the feedback we received from our members. It is to be noted that the recommendations are based on one industry sponsored RCT, which was not blinded and was carried out exclusively in private practice in the USA. There are concerns about the potential of other bias including programing bias, multiple patient contacts that could have influenced a favourable outcome and also an expectation of the participants that the new technology would yield better results.	Thank you for your comment. Please see the responses to comments 1, 30 and 134.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
40	35	Manufacturer	-	A major limitation of the Senza RCT is the concern of bias and lack of blinding. No attempt was made to blind the treatment allocation to patients or study investigators; patients knew which stimulator (high frequency or conventional low frequency) they received. The Senza RCT was a pre-market clinical study, sponsored by Nevro. Patients were randomized to a new treatment or the current available treatment and device programming was performed by industry representatives. Two investigators held significant equity interest in Nevro, as documented in the Summary of Safety and Effectiveness Data report, section X.E Financial Disclosure, publicly available on the FDA website. (6) Nevro indicates that an analysis was performed with and without these study data showing no impact on the outcome of the study (i.e. meeting the endpoint). Whilst the final outcome of the results was not swayed by these potential conflicts of interest, the points above, when combined, clearly suggest the potential for bias exists. Observer bias, industry sponsorship, and patient expectations are well studied and thus, results should be interpreted accordingly. **SEE APPENDIX 2 FOR REFERENCES**	Thank you for your comment. Please see the responses to comments 1 and 30. The EAC has reviewed the Financial Disclosure in the FDA SSED and noted the following statement: *"The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data."* The statement is considered particularly useful by the EAC for external and independent assurance from the FDA that the Senza RCT data was not considered biased by any personal financial conflicts of interest.
41	2	Patient	-	This was unblinded. Patients could have been blinded if they were randomized to one of two different types of SCS device and told they may experience tingling or other sensations.	Thank you for your comment. Please see the responses to comments 1 and 30. The EAC concluded that patient blinding using low frequency was not feasible because of the occurrence of paraesthesia in the comparator arm.
42	8	NHS Professional	-	Blinding and sources of bias in Neuromodulation studies: The EAC comment on the potential for bias in the Senza study, the main source of bias being the lack of blinding of the subjects. 2. Observer bias is a well-studied phenomenon. The observers could have been blinded in the Senza study but were not. In contrast De Andres et al blinded the observers to the nature of therapy. the impact of industry sponsorship needs to be taken into account; a recent paper entitled Head-to-head randomized trials are mostly industry sponsored and almost always favour the industry sponsor• finds that such studies report a result in favour of the sponsor in 96.5% of 57	Thank you for your comment. Please see the responses to comments 1 and 30.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				industry sponsored trials.	
43	19	NHS Professional	2.4	I have already dealt with the concerns I have with the suggestion that there is superiority of HF10kHz against conventional SCS. It is based upon the results of the SENZA-RCT. Although published in peer reviewed journals it is amazing to me that a study with such serious flaws has been accepted as representing such compelling evidence by the EAC. I believe that the lack of blinding and available patient and investigator bias makes such a conclusion based upon a single manufacturer sponsored non-inferiority designed trial for the right to market in USA unsafe. The expert commentary at the end of the 2 year SENZA-RCT by Professor Julie Pilitsis says - "A major limitation to this study is the lack of blinding. Although the improvement in visual analog scale was statistically significant, patients knew which stimulator (newer vs older technology) they received, inherently biasing their perceptions. Furthermore, the traditional stimulation that was used was not the latest generation of SCS offered. The statement "no paresthesia so treatment can be continued during sleep and while driving or operating machinery".	Thank you for your comment. Please see response to comment 7.

Clinical evidence: Interpretation of the evidence

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
44	20	Manufacturer	3.4	We are concerned that the critical statement about noted gaps in the evidence base is given insufficient emphasis in the draft consultation document. We believe that with the considerations emphasized in comments 7*, 65*, 37* and 37*, the limited evidence presented should only be considered either inconclusive or, at best, of very low quality that is insufficient for supporting a recommendation of superiority.	Thank you for your comment. Please see the responses to comments 7, 37 and 65.
45	20	Manufacturer	4.1	acknowledged that the single-arm studies reported similar findings We feel the guidance would be improved if the committee were to consider additional observational• studies that do not replicate Senza RCT study as indicated above in comment 37* (3.3; 1-3.).	Thank you for your comment. Please see the response to comment 37.
46	28	Society	-	In summary while we believe there is evidence that Senza is effective, the clinical evidence concerning its superiority to low frequency SCS or not is mixed. Because the economic case hinges on superior efficacy, and a comparison with what we feel is the wrong comparator technology, it is also open to question. Senza certainly has a place in the armoury of neuromodulation techniques, but on present evidence the simple statement in the draft document that Senza "works better and costs less" cannot be justified.	Thank you for your comment. Please see the responses to comments 7 and 143.
47	29	Manufacturer	-	The draft guidance deserves further deliberation with particular attention to the claim of sustained and long-term improvement in pain relief and function• in section 2.4. It is apparent from the recently published and presented evidence that HF10 is not able to generate sustained improvement in a sizeable proportion of patients. All of the evidence must be taken into account. - Real world evidence does not corroborate the single randomised trial that appears to have been influential in guidance development. - Many economic model inputs need to be re-validated and revised to reflect real-world experience.	Thank you for your comment. Please see the response to comment number 1.
48	30	NHS Professional	-	Has all of the relevant evidence been taken into account? I am reassured that all relevant clinical data has been presented. As the main document mentions we would wish to see the longer-term	Thank you for your comment. .

*The comment numbers have been amended to refer to the correct comment in the collated comments table.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				outcomes (i.e. 3,5, and eventually 10 years), and as such an ongoing audit and compulsory outcome reporting on a national level (if such a system of reporting exists) should be undertaken in units which are already using (or plan to use) the Senza stimulator.	
49	30	NHS Professional	-	Are the recommendations sound and a suitable basis for guidance to the NHS? Yes. No comment.	Thank you for your comment.
50	35	Manufacturer	-	Other considerations Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence? For the evidence presented the claims are reasonable however new studies, including blinded RCTs suggest a significant degree of uncertainty that the Senza device has significantly greater clinical benefits compared with conventional SCS systems. In addition, there is a significant degree of uncertainty associated with the EAC's determination of the Senza evidence as "strong". The economic model is limited, and the out of date, extrapolated cost data used to inform the model and associated commentary does not present sufficient rigour to justify the savings claims presented and thus provide solid evidence to inform NHS decision making.	Thank you for your comment please see the responses to comments 1, 143 and 144.
51	35	Manufacturer	-	Other considerations Are the provisional recommendations sound, and a suitable basis for guidance to the NHS? No, we do not believe that the provisional recommendations are sound on the following basis: • The findings of one RCT, which has a high risk of performance and detection bias, as highlighted in the EAC assessment report, have been extrapolated to a class of SCS rather than the comparator within the RCT. • Subsequent studies have generally not been able to replicate those results.	Thank you for your comment. Please see the responses to comments 7. The EAC considered 3 new studies to be within scope; De Andres et al. (2017), Al-Kaisy et al. (2017) and Van Buyten et al. (2017). The De Andres et al. (2017) study could not be used to update the cost model as the study did not report the proportion of patients who were responders, nor did it provide patient level data with which this could be calculated. Therefore the EAC advised that this study should be considered in terms of implications for

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				• Input of results from three recent studies, that have been published after the EAC concluded their assessment, may significantly alter the economic model outputs and conclusions regarding resource savings. • The battery technologies within the field of Complex Implantable Electronic Device (CIED) is constantly in development, as has been illustrated by recent MTG reviews (MTG 33) therefore a decision based on historical battery longevity is not sufficiently robust to inform decision making in the NHS. • The use of rechargeable devices has a place in clinical practice, however this has been limited to date due to the budget impact within the annual NHS budget cycle post TA159, as non-rechargeable devices have a lower acquisition cost We welcome recommendations on rechargeable technologies which extend device life, reduce patient complications and reduce battery changes, as a class approach rather that the limited comparative approach presented here. Assumptions in the economic model are based solely on the one Senza RCT. Subsequent studies have generally not been able to replicate those results. Input of results from more recent studies may significantly alter the economic model outputs and conclusions regarding resource savings. We suggest that results from subsequent publications be tested in the model using a weighted average for trial success, optimal pain relief, complication rates and explant rates. New studies, including blinded RCTs suggest a significant degree of uncertainty that the Senza device has significantly greater clinical benefits compared with SCS systems. In addition, they suggest a significant degree of uncertainty associated with the Committee's determination of the Senza evidence as "strong". Regarding the benefits to patients claimed for HF10 compared with low frequency SCS, several critical factors have not been addressed. First, these claims are based on one single RCT of HF10; (1) whereas traditional SCS has a long history of multiple RCTs and cohort studies, as well as systematic reviews and meta-analyses demonstrating a statistically significant, as well as clinically meaningful improvement in	patient benefits only, separate from cost considerations. The committee acknowledged that some of the evidence was on older devices but concluded that all the relevant evidence has been taken into account.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				pain and function.15 In this single premarket RCT of HF10. (1) a number of limitations should be noted. The study used an active control and made no attempts to blind subjects or clinical staff, which introduced the potential for bias. Investigators were allowed to adjust patients' oral analgesic medication usage after device activation, as necessary, which may potentially confound the effects of SCS with opioid therapy, as well as other pain medications (e.g., pregabalin). The authors failed to address whether changes in opioid medications could have impacted results. Both groups achieved a minimal clinically important difference in pain scores from baseline to follow-up and when looking at subject satisfaction (both "Satisfied" and "Very Satisfied" combined), results are similar, with 83.5% in the HF10 group and 83.1% in the traditional SCS group. Subsequent post-market studies of HF10 therapy have not demonstrated the same responder rates as this premarket clinical study.16,17 Research suggests that RCTs often cannot confirm the level of response from open label studies; however contrary in this case, the subsequent open label studies are unable to replicate the results of this single premarket RCT. Further research is required to confirm the replicability of results with HF10 therapy. **SEE APPENDIX 2 FOR REFERENCES**	

Population

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
52	2	Patient	-	It is not the case that one treatment mode treats neuropathic pain. NICE cannot extrapolate the results of one study on failed back surgery syndrome to all neuropathic pain states.	Thank you for your comment. The Committee acknowledged that most of the evidence for Senza was in people with failed back surgery syndrome and predominantly either chronic back or leg pain. The committee decided to amend section 1.2 and 4.4 to better reflect the most appropriate population.
53	4	NHS Professional	-	It would be advantageous to include documented evidence on the diagnosis of neuropathic pain, and which tools may be appropriate as part of that assessment.	Thank you for your comment.
54	6	NHS Professional	-	The Senza RCT was conducted on a population of patients with intractable pain of the trunk and/ or limbs. The various pain diagnoses listed in table 1 of Kapural et al. 2016 present a mixture of nociceptive, mechanical and neuropathic pain conditions. We have found no evidence in the publications of the Senza study to suggest that the study population underwent a neuropathic pain evaluation questionnaire or examination to provide evidence that these patients indeed suffered with neuropathic pain. Although a neurological examination was performed at baseline no findings were subsequently reported. FÃ¶rster et al (1) studied the nature of back pain in a cohort 1083 adults. They reported that a neuropathic pain was the predominant component in only 12% of patients with low back pain without surgery and in 15.2% following lumbar spine surgery. We therefore find no clear evidence to support the conclusion that patients recruited in the Senza study suffered with neuropathic pain predominantly. To our knowledge there is, to date, no strong evidence supporting the use of the Senza device in other neuropathic pain populations such as diabetic neuropathy or complex regional pain syndrome in contrast to conventional stimulation where a number of RCTs(2-6) have shown its effectiveness in the management of FBSS, complex regional pain syndrome and painful diabetic neuropathy. WE note that the EAC state that any conclusions or recommendations drawn from this assessment report should be limited to populations with leg and back pain of suspected neuropathic origin only. Despite this we note that Senza is to be considered for patients who are eligible for spinal cord stimulation as described in NICE technology appraisal guidance 159	Thank you for your comment. Please see response to comment number 52. The EAC reviewed the references outlined in your comment and with the exception of Kapural et al. (2016) the EAC deemed them all out of scope for this evaluation. Please see section 2 of the advisory document for further details. Forster M, et al. (2013) and Kemler MA, et al. (2001) are abstracts. The EAC excluded all conference abstracts from the assessment report and the advisory document (please see section 2 for more details) as they did not provide sufficient detail of the study. De Vos CC, et al. (2014) was excluded at the assessment report stage as wrong population. Slangen et al. (2013) was the wrong population (diabetic peripheral neuropathy) and intervention (not Senza). Van Beek M, et al. (2015) is the 24 month follow-up from the Slagen et al. (2013) study. Kemler et al. (2006) is the 5 year follow from the Kemler et al. (2001) study, which used the wrong population

				i.e. neuropathic pain. While we agree that there is evidence justifying the use of Senza in Back pain and FBSS we believe that a blanket recommendation for neuropathic pain with its various aetiologies is premature . 1.Forster M, et al. Axial low back pain: one painful area--many perceptions and mechanisms. PLoS One. 2013;8(7):e68273. PubMed PMID: 23844179. PMCID: 3699535. Epub 2013/07/12. eng. 2. Kemler MA, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. The New England Journal of Medicine. 2001 Aug;343(9):618-24. 3. de Vos CC, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial. Pain. 2014 Nov;155(11):2426-31. 4. Slangen R, Pluijms WA, Faber CG, Dirksen CD, Kessels AG, van Kleef M. Sustained effect of spinal cord stimulation on pain and quality of life in painful diabetic peripheral neuropathy. Br J Anaesth. 2013 Dec;111(6):1030-1 5. van Beek M, et al. Sustained Treatment Effect of Spinal Cord Stimulation in Painful Diabetic Peripheral Neuropathy: 24-Month Follow-up of a Prospective Two-Center Randomized Controlled Trial. Diabetes Care. 2015 Sep;38(9):e132-4. 6. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Spinal cord stimulation for chronic reflex sympathetic dystrophy--five-year follow-up. N Engl J Med. 2006 Jun 1;354(22):2394-6	(CRPS) and original study date precedes Senza.
55	6	NHS Professional	-	Overall I am troubled by the blanket recommendation of the Senza device based on a single RCT sponsored by the applicant manufacturing company in the presence of another independent RCT of similar design and longer follow up that contradicts these findings . My experience of 20 years in Spinal Cord Stimulation implants is more aligned with the results of the independent study than the Senza study which presents excellent results that no UK practitioner has been able to replicate in every day practice. Further troubling is the setting and population of the Senza study which is a clinically opaque mix of failed back surgery and low back pain with no accurate clinical description. Finally the number of small studies published in the filed on higher frequency have been unable to replicate such effects , blinded studies have found no difference from placebo.	Thank you for your comment. Please see the responses to comment numbers 52 and 54.

				In view of the above, and the absence of a clear mechanism of action, it may be premature to consider such a blanket recommendation There is a clear need for the NIHR to consider funding an independent UK trial comparing the Senza device to other device before considering a definitive blanket recommendation. Finally NIHR RfPB have recently confirmed funding of a double blinded placebo controlled trial of the Senza device use in Low back Pain of Neuropathic origin , it would be helpful for the committee to examine the protocol as well as any preliminary work from the above study.	
56	8	NHS Professional	-	WE note that the EAC state that any conclusions or recommendations drawn from this assessment report should be limited to populations with leg and back pain of suspected neuropathic origin only. Despite this we note that Senza is to be considered for patients who are eligible for spinal cord stimulation as described in NICE technology appraisal guidance 159 i.e. neuropathic pain. While we agree that there is evidence justifying the use of Senza in Back pain and FBSS we believe that a blanket recommendation for neuropathic pain with its various aetiologies is without evidence and not in patients best interest. It is important for patients and physicians to have the choice of device/frequency of SCS.	Thank you for your comment. Please see the responses to comment numbers 52 and 54.
57	15	Society	-	Are the provisional recommendations sound, and a suitable basis for guidance to the NHS? The Senza RCT was on failed back surgery syndrome. This cannot be extrapolated to other neuropathic conditions.	Thank you for your comment. Please see the response to comment number 52.
58	19	NHS Professional	1.2	I note that the EAC state that any conclusions or recommendations drawn from this assessment report should be limited to populations with leg and back pain of suspected neuropathic origin only. Despite this I note that Senza is to be considered for patients who are eligible for spinal cord stimulation as described in NICE technology appraisal guidance 159 i.e. neuropathic pain. While I agree that there is evidence justifying the use of Senza in Back pain and FBSS I believe that a blanket recommendation for neuropathic pain with its various aetiologies is premature. Furthermore I note that the Senza study was conducted exclusively in US private practice centres. It is unclear to me how the trial intervention or control devices were funded or whether the recruited subjects would have accessed these devices outside the study. The USA lacks comprehensive healthcare coverage for SCS, unlike the UK, where policy is clear that SCS is available to all patients who are deemed appropriate. The	Thank you for your comment. Please see the responses to comment numbers 1, 52 and 54.

				mechanism of funding of the study devices is relevant since it may have contributed to the extraordinary result of the study. The Senza-RCT was funded by Nevro only. I believe that this may impact the generalisability of the study results into the NHS. For example, The SENZA-RCT excluded patients on worker's compensation.	
59	19	NHS Professional	4.5	It is not clear if HF10kHz SCS is effective in other neuropathic pain states. I don't think this can be assumed. Certainly no claim of superiority can be made.	Thank you for your comment. Please see the responses to comment numbers 52 and 54.
60	32	Society	-	The SENZA study has been carried out in patients with back pain following FBSS, but the MTEP has recommended that SENZA is better for all neuropathic pains. It has been observed that majority of FBSS back pain do not have a predominantly neuropathic component; the SENZA study do not mention about using appropriate tools to screen for the severity of neuropathic pain. We feel that the extrapolation of the recommendation to cover all neuropathic pain is based on poor study criteria.	Thank you for your comment. Please see the responses to comment numbers 52 and 54.

Characteristics of the technology: Battery charging

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
61	4	NHS Professional	-	Patients who have previously experienced low frequency SCS are reassured by the feeling of paraesthesia as documented. Patients with low frequency SCS are also used to a charge interval (depending on SCS usage/setting etc) of 7days-2 weeks. Patients with HF10 systems need to understand the importance of daily charging, which is seen as an inconvenience in some patients. A poor charging pattern can lead to poor therapy satisfaction as patients run the battery flat and switch off therapy accidentally.	Thank you for your comment. Please see section 4.10 of the guidance which highlights recharging frequency.
62	20	Manufacturer	4.1	The clinical experts explained that patients prefer non-rechargeable SCS devices because of the inconvenience of regular charging, which can be time-consuming. There appear to be no data on patient perspectives and preferences regarding differences amongst spinal cord stimulators in device charging characteristics. It is certainly plausible that patients prefer devices that do not need to be charged frequently " for example, 30-45 minutes daily " and that such preferences could potentially offset any discomfort or inconvenience associated with paraesthesia, mapping, or battery replacement. However, such anecdotal reports and speculation do not substitute for evidence.	Thank you for your comment. The committee makes recommendations after considering all of the relevant evidence including expert advice. The committee considered your comment carefully and decided to amend section 4.10.
63	28	Society	4.1	It should be noted more prominently that the recharging burden with this system is far higher than with other rechargeables (45 mins every day according to the companys own literature, compared to perhaps once a week with other systems). Many patients do not want to recharge for this length of time every day. Audits show that long term explant rates are higher with rechargeable systems, presumably because the recharging burden negatively affects therapy satisfaction. In addition, daily deep-cycling of rechargeable batteries might be expected to cause their capacity to degrade rapidly, and in view of the lack of long term follow up the true longevity of these systems in practice is unproven. The committee may like to consult an expert in battery technology for an independent view, and/or survey UK centres to assess experience so far (i.e. have batteries had to be replaced yet?).	Many thanks for your comment. Please see responses to comment numbers 4 and 61. The EAC explored concerns regarding battery longevity and charging and considered the company claims of 10 and 25 years of battery life, for higher and lower power stimulation settings, respectively, to be supported by the technical evidence provided (CiC) (please see section 6.1 of the advisory document for further details).
64	35	Manufacturer	-	Other considerations Recharge Burden An additional important factor to be considered is the increased recharge burden on the patient associated with the increased energy requirements	Thank you for your comment. Please see the responses to comment numbers 1, 61 and 63. The studies in your comment; Smith et al. (2015) and Kriek et al. (2017) were excluded by the

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				of HF10 therapy. HF10 patients are required to recharge their neurostimulator daily (average of 45 minutes) (11) compared to conventional SCS (average 5.2 times per month). (11,2) Similarly, the PROCO RCT showed that all frequencies provided equivalent improvement in pain relief, but battery efficiency was three times greater with 1kHz versus 10khz stimulation (Thomson 2017). (3) Daily recharging could affect patient satisfaction, convenience, or even interfere with daily activities. The frequent recharge burden required for higher energy dose SCS therapy (like HF10) can make lower-frequency SCS preferable to some patients. (Smith et al 2015) (12) These considerations are aligned with publications and clinician feedback that some patients require switching between stimulation frequencies to maintain pain relief and others prefer the sensation of paraesthesia (see Nevro Supporting Documentation, Section 8 Patient selection and acceptance). In a multicentre, non-randomized, prospective study by Rapcan et al (2014) (13) found nearly a quarter of patients unable to maintain satisfactory pain relief with HF SCS or conventional SCS and needed to switch between the two programs every 4-5 weeks. In a double-blind, randomized and placebo-controlled crossover trial by Kriek et al (2017), (14) patients with Complex Regional Pain Syndrome (CRPS) were randomized to a crossover of 5 different stimulation settings (4 0 Hz, 500 Hz, 1200 Hz, Burst and placebo). The authors found all active stimulation settings were equally effective in relieving neuropathic pain and significant pain reduction was achieved with all settings when compared to placebo. However, 48% of patients preferred the standard 40-Hz stimulation, whereas 48% were split across one of the other active stimulation settings (1 patient preferred placebo). More patients found conventional 40 Hz stimulation to be more comfortable and have the best user-friendliness compared to the other settings. Importantly, the authors conclude that stimulation preference did not solely rely on pain relief, but other factors such as comfort and user-friendliness are involved. **SEE APPENDIX 2 FOR REFERENCES**	EAC at the assessment report stage. Rapcan et al. (2014) (cited as 2015 in the assessment report) is already included in the assessment report. Please see section 2 of the advisory document for further details.

Characteristics of the technology: High frequency definition

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
65	20	Manufacturer	1.1	it (high frequency spinal cord stimulation) is associated with better pain control than low frequency spinal cord stimulation• We respectfully request that the committee reconsider its stated definitions of low and high frequency, since these definitions are not supported in the vast bulk of available literature. The recommendations, as currently drafted, state that 'high frequency stimulation• refers to a single device (Senza), while 'low frequency stimulation• refers to all other existing devices that are not Senza. It is disappointing that there is no recognition of the body of literature, outlined in the table (list) below, which defines 'high frequency• as a range between 500 and 10,000 Hertz and not specifically and only 10,000 Hertz. Likewise, for low frequency, we think it is regrettable that the guidance did not consider a paper published in Neuromodulation (Deer et al., 2014) and by the International Pain Societys Neuromodulation Appropriateness Consensus Committee (NACC), which indicates that standard SCS frequency ranges from 30 to 300 Hz. Table 1 Frequency (Reference) 500 Hz (Song, Viisanen, Meyerson, Pertovaara, & Linderoth, 2014) 500 Hz (de Vos, Bom, Vanneste, Lenders, & de Ridder, 2014) 500 Hz (Van Havenbergh, Vancamp, Van Looy, Vanneste, & De Ridder, 2015) 500 Hz (Kriek, Groeneweg, Stronks, & Huygen, 2015) 1,000 Hz (Youn, Smith, Morris, Argoff, & Pilitsis, 2015) 1,000 Hz (Van Havenbergh et al., 2015) 1,000 Hz (Johanek JM, 2014) 1,000 Hz (Song et al., 2014) 1,200 Hz (Kriek et al., 2015) 500, 1,000, 10,000 Hz (Song et al., 2014) 10,000 Hz (Kapural et al., 2015) Additionally, we would also request that the committee acknowledges that the superiority of the isolated frequency 10 kHz is not substantiated by the clinical evidence. Comparing the most recent data available, there are	Thank you for your comment. Please see the response to comment number 1. The committee carefully considered your comment and decided to amend the guidance to further clarify the technology being evaluated.

<table>
<tr><th>Comment no.</th><th>Consultee ID</th><th>Role</th><th>Section</th><th>Consultee comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>three RCTs that looked at 10 kHz versus other frequencies. The only study that concluded that 10 kHz is superior is an un-blinded US study funded by Nevro. A recent European RCT (De Andres et al., 2017) compared Nevro 10kHz to standard rate SCS and concluded that pain and functional outcomes out to 1 year were the same for HF10 and standard rate. In the UK, the PROCO RCT (Thomson, 2017) compared 1 kHz, 4 kHz, 7 kHz, and 10 kHz using a robust double-blind crossover design. The PROCO RCT concluded that there was no difference in pain or functional outcomes between frequencies, although 1 kHz used significantly less energy (and was therefore more efficient) than 10 kHz. In summary, two of three RCTs conclude that 10 kHz is NOT superior to other modes of SCS.

Therefore, we believe that when considering existing clinical literature as well as the most recently available high quality published evidence, the conclusion that the Senza device is the only one capable of delivering high frequency stimulation that provides better pain control is unsubstantiated and we request that this conclusion is redacted.

SEE APPENDIX 1 FOR REFERENCES</td><td></td></tr>
<tr><td>66</td><td>20</td><td>Manufacturer</td><td>2.1</td><td>Definitions “ 'High Frequency SCS• and 'Low Frequency SCS’

We feel it is regrettable the draft guidance does not recognise that frequency is only one variable parameter which can affect a patients outcome. We also feel it is important to highlight that 'frequency• is not a type of device and should not be considered in isolation. We would request that you take into account that spinal cord stimulation devices on the market today, deliver an electrical stimulation that are programmed using varying settings that include frequency, pulse width and amplitude to achieve optimal pain relief. Since no pain patient presents with exactly the same pain patterns or severity, best practice therapy is determined by combining these different parameters. Table 2 details the published parameters of currently available spinal cord stimulation devices. Since all devices on the market have the ability to program the devices across a range of frequencies (Table 2), we would suggest it is inaccurate to define the Senza device as high frequency and all others as low frequency.

Table 2
<table><tr><td></td><td>BSC Precision</td><td>BSC Spectra</td><td>Nevro</td><td>Abbott</td><td>Medtronic</td></tr></table></td><td>Thank you for your comment. Please see the response to comment number 1 and 65.
NICE medical technologies guidance evaluates a single medical technology based on the claimed advantages of introducing the specific technology compared with current management of the condition. It is not a multiple technology assessment and does not compare evidence for all similar technologies in a broader class. These principles are described in further detail in the Medical Technologies Evaluation Programme methods guide, The EAC reviewed the Koulosakis (2017) and excluded it on basis of wrong device (Precision Plus High Rate with Multiwave Technology (Boston Scientific, Valencia, CA, USA)) and it</td></tr>
</table>

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				<table><tr><td>Amplitude</td><td>0-20 mA</td><td>0-25.5 mA</td><td>0-15 mA</td><td>0-25.5 mA</td><td>0-10.5 volts</td></tr><tr><td>Pulse Width</td><td>10-1,000 Î¼s</td><td>20-1,000 Î¼s</td><td>20-1,000 Î¼s</td><td>50-500 Î¼s</td><td>60-1,000 Î¼s</td></tr><tr><td>Frequency</td><td>2-1,200 Hz</td><td>2-1,200 Hz</td><td>2-10,000 Hz</td><td>2-1,200 Hz</td><td>2-1,200 Hz</td></tr></table> Finally, we would respectfully suggest that the committee review the latest scientific research which demonstrates that the clinical observations from the 10 kHz stimulation devices are not caused by the stimulation frequency, and in fact, very high frequencies are not required to achieve the results observed. Instead, the same clinical outcomes can be obtained at lower frequencies (1 kHz) with proper adjustment of amplitude, pulse width and electrode selection, still within sub-paraesthesia levels. In particular, Thomson (2017) and Koulosakis (2017) have all demonstrated that the same pain outcomes obtained at 10 kHz can be obtained as well at lower frequencies (1 kHz, 1.2 kHz and 2 kHz). Their experience did not find the floor of frequencies (how low the frequency can be) to still observe the same outcomes, but we know that at least 1 kHz can provide the same outcomes, while significantly reducing the recharging required of 10 kHz. The clinical conclusion is that frequency alone is not the determinant of the outcomes but the proper adjustment of electrode selection, frequency, pulse width and amplitude. **SEE APPENDIX 1 FOR REFERENCES**	was a case series of n=3 patients. The EAC excluded all conference abstracts from the assessment report and the advisory document (please see section 2 for more details) because they did not provide sufficient detail to assess the study.
67	20	Manufacturer	2.1	Senza can deliver low frequency SCS (2 to 1,200Hz), but it is also able to provide a novel high frequency treatment called HF10 therapy• According to the definition of frequency provided by Nevro, low frequency refers to '2 to 1,200 Hz• range, which conveniently encompasses the range of frequencies available from other manufacturers devices (See Table 2 above). We are concerned that this definition is not supported by the scientific literature (See Table 1 above). We would also like to highlight that there are no references reported within the consultation document that support the definitions of high and low frequency provided by Nevro and would be concerned if, once published in NICE guidance, the NHS were to assume these definitions were clinically correct. We believe it would be helpful if this deficit were flagged within the guidance.	Thank you for your comment. Please see the response to comment number 65.
68	23	NHS Professional	2.1	NEVRO SCS has far inferior programming capabilities in the conventional frequency range and the claim that it can deliver 2-1200 Hz to the same quality that other systems (designed specifically for this purpose) is not true.	Thank you for your comment. Please see the response to comment number 65.

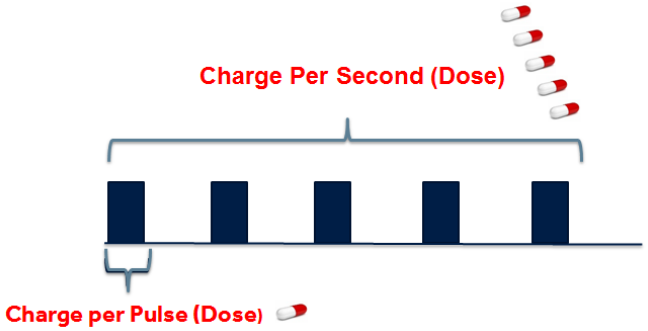
Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				The system is developed to work at fixed frequency of 10K without reliance on mapping the area of the pain or feeling of tingling hence performs best only at this fixed frequency. The company reps actively discourage the users from use of low frequency.	
69	26	Manufacturer	-	Regarding the proposed title of this guidance: All the evidence considered has studied the safety, clinical efficacy, and cost-effectiveness of 10kHz SCS using HF10 Therapy waveform and frequency. The term high frequency• is not sufficiently descriptive because it does not reference any particular SCS therapy. We therefore suggest that High Frequency• should be changed to read HF10 Therapy• to reference the 10kHz frequency. This would also align with the product description and be consistent with descriptions used elsewhere in the consultation document.	Thank you for your comment. Please see the response to comment number 65.
70	26	Manufacturer	-	All the evidence considered has studied the safety, clinical efficacy, and cost-effectiveness of 10kHz SCS using HF10 Therapy waveform and frequency. The term high frequency• is not sufficiently descriptive because it does not reference any particular SCS therapy. We therefore suggest that High Frequency• should be changed to read HF10 Therapy• to reference the 10kHz frequency. This would also align with the product description and be consistent with descriptions used elsewhere in the consultation document.	Thank you for your comment. Please see the response to comment number 65.
71	28	Society	-	Senza is one system capable of delivering paraesthesia-free therapy but it is not the only one to do so. In places the document appears to dichotomise SCS as on the one hand Senza/high-frequency/paraesthesia-free, versus on the other hand low-frequency/paraesthesia-generating; but high frequency is not necessary for paraesthesia freedom, it is simply one way of achieving it. In other words, paraesthesia-free operation is not unique to Senza and low frequency stimulation does not necessarily imply that there will be paraesthesia.	Thank you for your comment. Please see the responses to comment numbers 65 and 66.

Characteristics of the technology: Mode of action

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
72	19	NHS Professional	4.6	This statement is simply incorrect. Every proposed mechanism of action of HF10kHz has been shown to be incorrect. But this is in the nature of scientific discourse. As yet no different mechanism beyond GABA inhibition has stuck.	Thank you for your comment. The committee decided to amend section 4.6, to acknowledge the lack of knowledge around the mode of action.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Animal work by Schechter, Song showed equivocal pain suppression responses between 50Hz, 1kHz and 10kHz. Recently Li and Linderoth showed better pain suppression effects 1kHz compared to 50Hz and 10kHz. Neuromodulation 2017 - early view	
73	26	Manufacturer	-	Expert opinion has characterised differences in the mechanism of action for HF10 versus low frequency SCS devices and this is backed by published and ongoing studies. Firstly, HF10 therapy is the only SCS device which produces pain relief independent of paraesthesias. Neither mapping of paraesthesia during electrode placement nor delivery of pain relief with HF10 therapy ever involves paraesthesia. This is unique to HF10 therapy and supports the fundamentally different mechanism of action as explained by De Carolis et al 2017 (Pain Physician 2017; 20:331-341). Additionally, ongoing studies at Kings College London by Dr Stephen McMahon have concluded that 10 kHz SCS had no observable effect on Dorsal Column axon performance. Furthermore 10 kHz SCS, but not 1 kHz SCS, reduced the excitability of lamina I pain projection neurons compared to sham. These studies provide evidence supporting the significant difference in mechanism of action between HF10 therapy and low frequency SCS which relies on activation of dorsal columns. Interim results from this work were presented as a poster at the International Neuromodulation Society meeting in Edinburgh in May 2017. This poster presentation has been shared with NICE by email as part of this consultation process.	Thank you for your comment. The De Carolis et al. (2017) paper was excluded by the EAC in the initial literature search on the basis of population and reported outcomes. The INS poster was excluded by the EAC as animal studies were excluded from the evaluation.
74	28	Society	-	These comments are submitted on behalf of the board of NSUKI, the Neuromodulation Society of the UK and Ireland. NSUKI is the body which represents UK and Irish medical professionals who provide neuromodulation, i.e. the use of implanted stimulator systems including spinal cord stimulators to treat conditions including chronic neuropathic pain. Our membership is predominantly Consultant Anaesthetists and Neurosurgeons. Spinal cord stimulation (SCS) is the most commonly performed type of implanted stimulator for pain relief. It is described in detail in the 2008 NICE technology appraisal guidance document TA159 Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (referred to below for brevity as TA159), updated 2014. This document described fourteen systems from three different manufacturers that were CE marked and marketed at the time, and provided a contemporary review of the	Thank you for your comment. NICE medical technologies guidance evaluates a single medical technology based on the claimed advantages of introducing the specific technology compared with current management of the condition. It is not a multiple technology assessment and does not compare evidence for all similar technologies in a broader class and will not supersede NICE technology appraisal guidance on spinal cord stimulation.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				evidence and an economic assessment of SCS. At the time TA159 was written, SCS systems all delivered a regular pattern of stimulus pulses to the spinal cord at a low frequency, generating paraesthesia which was generally believed to be a prerequisite to achieving satisfactory pain relief. It is now abundantly clear that this long held view was incorrect, and paraesthesia is not necessary for pain relief. Senza is one device which has demonstrated this. The mechanisms of SCS of any type are not understood with any certainty. Whilst it seems likely that Senza will have mechanistic differences to paraesthesia-generating SCS, so too will other new devices and we do not understand the basis for singling out Senza from other forms of SCS for an individual NICE policy document. Is there a plan to introduce a separate document for each new SCS device type? In our view a comprehensive revision of TA159 to include all new varieties of device (of which there are now several) would be greatly preferable. This should include Senza (Nevro) but also for example High Density (Medtronic), other paraesthesia-free systems (Abbott, Boston Scientific), and closed loop SCS (Saluda).	These principles are described in further detail in the Medical Technologies Evaluation Programme methods guide, and in the block of text at the beginning of the medical technology guidance. This text states that the case for adoption is based on claimed advantages of introducing the specific technology compared with current management of the condition. It also states that the specific recommendations in the medical technologies guidance on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages.
75	35	Manufacturer	-	Model inputs Senza device and HF10 therapy is not distinct and separate from conventional SCS HF10, as currently marketed, is only one of several options that can be tailored to achieve optimal clinical outcomes for patients in this complex area. We suggest that there is not strong evidence to recommend that HF10 is significantly different, in terms of patient outcomes, to the technologies reviewed in TA159 and therefore does not require separate Medical Technology Guidance. Miller et al (2016)(11) presented basic concepts of energy delivery (amplitude, frequency and pulse width) and published evidence supporting the conclusion that SCS programming can be thought of as a combination of these factors that deliver a “dose” of SCS therapy. The historical view of SCS programming strategies has considered amplitude, frequency and pulse width as separate and discrete variables. 10 kHz is a recent stimulation concept of delivering stimulation using a specific set of parameters, but still focuses on energy delivery (a combination of amplitude, frequency and pulse width).	Thank you for your comment. Please see the responses to comment numbers 69 and 74. The EAC excluded the Miller et al. (2016) study at the assessment report stage as Senza was not used. Please see section 2 in the EAC’s advisory document for further details.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Pulse width is the sustained delivery of a specific amount of current amplitude for a specific amount of time and when multiplied together creates a “charge per pulse”. The authors highlight the strength-duration curve which shows that narrow pulse widths require high amplitudes to activate a neuron, whereas wider pulse widths need lower amplitudes. New concepts focus on the combination of parameters and their resulting charge delivery. “Charge per second” is the charge per pulse multiplied by the number of pulses delivered in 1 second. In a comparison between two different programming strategies, charge per pulse may be lower, but charge delivery over time can be considerably higher in one of the two. Duty cycle, or proportion of ON time the signal is active and delivering energy is a function of frequency and pulse width. Higher duty cycles can be achieved by simply varying pulse width and frequency. • 30 µs pulse at 10 kHz = 30% • 500 µs pulse at 500 Hz = 25% • 200 µs pulse at 1000 Hz = 20% • 400 µs pulse at 50 Hz (historically typical for conventional SCS) = 2% The authors use an analogy to explain that electrical that electrical energy can be delivered similarly to a medication with various dosing strategies characterized by its concentration (duty cycle), dose (charge per sec) and rate of delivery (current amplitude). The electrical energy is titrated to produce optimal pain relief.  	

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				It is a 'high dose' rather than the specifics of an individual parameter such as high frequency that may determine any claimed improvement on clinical outcomes versus the comparator of 'conventional' stimulation. This may be a potential explanation why recent RCTs comparing various levels of higher frequencies have subsequently failed to demonstrate a difference in patient outcomes. It is important to note that given the nature of the programmability of all medical devices in this field , frequency, pulse width and amplitude can all be varied to achieve higher doses of stimulation and similar clinical outcome to HF10 as evidenced by the PROCO RCT (3). Miller et al (11) conclude that the total charge delivery and the basic parameters of amplitude, pulse width and frequency all play an important role; thus, frequency is not the only important parameter.11 HF10 is simply another form of high dose, which can be achieved with other SCS manufacturer systems by manipulating these 3 basic elements.11 Thus, the difference between high and low frequency stimulation is an incorrect distinction to make given that frequency is only one part of the equation. To use an analogy from drug therapy as an illustration; there are many different strengths and formulations of analgesics which ultimately deliver similar levels of pain relief. The evidence to date suggests that a range of programmable features are required to optimise clinical outcomes in this complex patient group. Pain is a unique and highly individualised experience and thus requires a personalized approach in order to achieve continuous pain relief. Thus, we believe that HF10 as currently marketed is only one of several options that can be tailored to achieve optimal clinical outcomes for these complex pain patients. We suggest that there is no strong evidence to recommend that HF10 is significantly different, in terms of patient outcomes or stimulation dose, to the technologies reviewed in TA159 and therefore does not require separate Medical Technology Guidance. **SEE APPENDIX 2 FOR REFERENCES**	
76	18	Manufacturer	-	It is also surprising that 10kHz stimulation is being singled out as being different to other forms of SCS when the reason as to why it may be different is a mystery. The mechanism of action of SCS is largely understood, that there may be a different MOA for 10kHz is not	Thank you for your comment. Please see the responses to comment numbers 65, 72 and 74.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				understood, at all. It is hard to imagine that this form of therapy would have a radically different MOA to any other SCS system when the materials, form of therapy and therapy target are identical. i.e. Platinum iridium contacts - delivering electricity in a charge balanced bi-phasic pulse " driven by a constant current controlled generator " which contains standard SCS electronics " to the axons of passage running up and down the dorsal columns of the spinal cord.	

Characteristics of the technology: MRI

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
77	32	Society	-	The SENZA kit is not MRI compatible and limits its use in patients who would need MRI scans for evaluation; there is a move towards MRI compatible kit to ensure patient safety as well as a better financial option.	Thank you for your comment. Please see section 6.2 of the advisory document. Senza is now CE marked as full-body MRI conditional, this extends to full-body MRI at 1.5T and head and extremity MRI at 1.5T and 3T.
78	5	NHS Professional	-	MRI conditionality is very important. Senza implanted patients can only have head and extremity MRI under very strict conditions. If a patient with Senza device needs an MRI on spine (Cervical, Thoracic or Lumbar) one needs to remove the leads from epidural space and reimplant the patient later on. This exposes the patients to avoidable surgeries and huge expenditure for NHS. About 70% patients with Spinal cord stimulator implant may need MRI at some stage in their life. Other manufacturers have fully MRI conditional systems where a MRI can be performed on the spines as well with minimal artefacts.	Thank you for your comment. Please see the response to comment number 77.
79	19	NHS Professional	2.2	The Senza device was not compatible with MRI scanners at the time of economic model. We estimate that a number of these devices would have been explanted in order to allow the user to undergo a necessary MR examination. This is another example of a flawed economic analysis. Recently, Nevro have gained some degree of MRI conditionality. However the allowable power settings allowed for whole body MRI are, I am told,	Thank you for your comment. Please see the response to comment number 77.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				below those that would produce a useful image in a 1.5 Tesla. Expert advice from an MRI radiologist is advised	
80	35	Manufacturer	-	Other considerations MRI Compatibility The recent CE mark approval for expanded MRI labelling of Senza devices (http://www.prnewswire.co.uk/news-releases/nevro-receives-ce-mark-for-full-body-mri-conditional-labeling-with-the-senza-spinal-cord-stimulation-657795643.html) maintains some limitations compared to other MRI-compatible SCS devices. The recent Nevro expanded labelling applies only to percutaneous leads (surgical leads are still contraindicated for full body). This labelling applies only to 1.5 Tesla. There are 2 scanning body zones and SAR limits depending where the coil is positioned: • Zone A which is basically Torso scans: The average whole-body SAR shall be limited to 0.4 W/Kg and the head average SAR shall be limited to 0.64 W/kg. • Zone B which is head and extremity: 2 W/Kg (normal operating mode) and the head average SAR shall be limited to 3.2 W/kg (normal operating mode). The maximum active scan time is 30 minutes and scans should not be performed if an electrode contact is registering high impedance. These requirements fall under the reduced power category when it comes to MRI scans, and 1.5T may not provide an adequate image. With these limitations, MRI-compatibility remains inferior to other SCS systems currently available. We suggest that the impact of explants for the purpose of MRI be explored in the model.	Thank you for your comment. Please see response to comment 77.

Characteristics of the technology: Paraesthesia

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
81	19	NHS professional	2.4	Firstly Nevro have managed to demonise parasthesia. Many patients with neuropathic pain like the parasthesia. In my published UK series 70% either liked or were indifferent to parasthesia. It does not follow that patients prefer to turn off parasthesia to sleep. Look carefully at the Nevro recommendations for driving. There was no significant difference between the opioid usage in both arms of the Senza-RCT at 12 months Parasthesia mapping - Parasthesia mapping takes as long as it takes to put the anchoring sutures into the fascia in preparation for the fixation device. So there is no time saving. Secondly this marketing message is used to encourage the use of deep sedation or general anaesthesia so exposing patients to risk of complications of a prone anaesthetic (more frequent than supine positioning), neurological harm (no patient feedback) and finally no option to use parasthesia based SCS if HF10kHz fails as electrode contacts not in the correct place.	Thank you for your comment. Section 2.4 reflects the company's claimed benefits.
82	19	NHS Professional	4.3	Patients do not find parasthesia mapping "distressing and disorrientating". I routinely do SCS procedures under local anaesthesia with light sedation at the beginning. When asked if the procedure is better, same or worse than expected the answers are 75% better, 20% same and 5% worse. If the implanter uses general anaesthesia then perhaps patient may be disorientated due to the effects of the anaesthesia but NOT to the parasthesia testing. As stated before in my UK series of 321 registry patients over a 7.5 year follow up, patients were asked independently amongst other things about their feelings regarding parasthesia - 70% liked or were indifferent, 24% found mildly to moderately unpleasant and 1% severely unpleasant. Nowadays with non-Nevro devices a range of sub-perception programmes are used to provide pain relief without parasthesia perception. These include 1kHz, Burst and others.	Thank you for your comment. The committee considered this comment carefully and decided to change section 4.3 to further clarify its considerations on paraesthesia.
83	19	NHS Professional	4.15	The contention that the procedure is shorter is incorrect for the reasons stated above. Parasthesia testing is done during the period of surgical activity with anchoring suture placement. This all takes 10 minutes. Nevro leads also need to be anchored. Furthermore if leads are placed properly for both parasthesia based SCS	Thank you for your comment. The committee makes recommendations after considering all of the relevant evidence including expert advice. The committee heard from clinical experts who routinely implant both low frequency SCS devices and Senza devices as reported in section 4.6

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				and Higher frequency SCS, then the Nevro patients are being denied an alternative in those patients where HF10kHz does not work.	The committee decided to remove section 4.15.
84	20	Manufacturer	1.1	Avoid the tingling sensation that patients may experience with low frequency SCS• We are concerned that this statement appears to imply that 'paraesthesia• or 'tingling sensations• should be avoided, as if it was an unwanted effect of the so-called 'low frequency SCS• . Clinically, paresthesia is a tingling sensation that covers the anatomical area of pain, while sub- paraesthesia is simply the absence of the tingling sensation (also known as sub-threshold.) Sub-paraesthesia is a byproduct of programming parameters and can be created at a number of frequencies: “ 500 Hertz (de Vos et al., 2014) “ â‰¤1200 Hertz (North, Hong, & Cho, 2016) “ 10,000 Hertz (Kapural et al., 2015) We agree with what the committee heard (page 8; 4.3; line 9-11), that some patients find the paraesthesia reassuring and a means of confirming for themselves that the device is still working. For these patients, the Senza 'sub-perception• device may be distressing and disorienting for the patients, as they do not know whether the device is 'on• or 'off• . Paraesthesia, as well as sub-paraesthesia, is a subjective preference. We are disappointed that the guidance appears to assume that patients should or would prefer to 'avoid the tingling sensation• and believe the committee should consider the clinical evidence showing that multimodal SCS devices provide customization capabilities that support the need for patients to access both sub-perception and paraesthesia-driven SCS and urge the committee to reconsider this statement(Berg, Mekel-Bobrov, Goldberg, Huynh, & Jain, 2017; Kriek, Groeneweg, Stronks, de Ridder, & Huygen, 2017). **SEE APPENDIX 1 FOR REFERENCES**	Thank you for your comment. Please see the response to comment 82. The EAC reviewed the studies outlined in your comment. Kaprual et al. (2015) has already been considered in the assessment report. The remaining studies were excluded on the basis that Senza was not included in the study (please see section 2 of the EAC advisory document for more details).
85	20	Manufacturer	4.3	The clinical experts explained that paraesthesia mapping is routinely done when implanting low frequency SCS devices• Unfortunately, we feel that this statement is not entirely correct and too	Thank you for your comment. Please see response to comment 82. On hearing expert opinion on paddle leads the committee decided to amend

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				much weight may have been placed upon the opinion of a small number of clinical experts. While we fully recognise that this mapping is routinely used with percutaneous leads, paresthesia mapping is not mandatory for implanting low frequency SCS, and is not widely used when paddle leads are implanted. Our concern is that the draft guidance presents the non-use of paraesthesia mapping as being a wholly beneficial development and we feel this fails to acknowledge mappings benefits. There are several reasons why paresthesia mapping may be used and we respectfully request that the committed highlights this and the reasons for it in the guidance : - It offers a unique opportunity to confirm the lead placement is accurate and optimal at the time of the implant. - Paresthesia mapping avoids the need for repositioning the lead, in case post-operative stimulation is not effective. - Paresthesia sensations allow clinicians to assess in real-time whether the stimulation will be effective in targeting the pain area. - Stimulation settings that are used during the paresthesia mapping will be used for the post-op trial, reducing the need for intensive programming search after the lead placement procedure. - In some cases, on-table testing may allow physicians to implant the SCS device without the need for a post-operative trial, i.e. without the need for a second surgical procedure. We would also like to highlight that there are disadvantages to not conducting paraesthesia mapping, which would also be valuable to explain in the guidance as these would be important clinical considerations when making a choice about which device to offer a patient. Devices without paraesthesia mapping capability only rely on anatomical landmarks (radiographic vertebral levels) to position the lead under general anaesthesia (e.g., Senza percutaneous leads or low frequency paddle leads). As no intra-operative testing is possible, stimulation testing only happens after the implant, during the post-operative trial, and is used to assess the efficacy of the stimulation.	section 4.3 to further clarify paraesthesia mapping.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Retrospective studies (Russo et al., 2016) have shown 27% trial failure when using Senza, while others show 8% trial failure when using low frequency SCS. We would like to raise the question about whether the limitation of Senza lead placement (no possibility to do any on-table testing) would lead to higher trial failure rates. **SEE APPENDIX 1 FOR REFERENCES**	
86	20	Manufacturer	4.3	"and that this increases procedural time and complexity." We have been unable to identify any specific clinical evidence that supports this statement. It is particularly important because procedural times and complexity were not assessed in the outcomes used during the evaluation. Given that the economic model did not include costs beyond those of the devices, it is of concern that this information has been given such prominence in the guidance particularly as the Senza RCT did not find any statistical significance in patient satisfaction. Given that there is no data presented in the guidance to substantiate this suggestion, we respectfully suggest it should be removed. If to be compared, procedural times should include all components of the total SCS lead implant procedure, and not only the very specific intra-operative step of using paraesthesia mapping or not. For example, comparing 'asleep procedure" (Senza) with 'awake procedure (paraesthesia mapping) should consider the different anaesthetic conditions and their impact on the procedural time and complexity. Offering an 'asleep• procedure may require additional patient preparation and induce additional costs (anaesthesia and vital signs monitoring equipment; drugs/gauze used, theatre staff member to monitor the patient during the procedure, post-operative wake-up and recovery phase.).	Thank you for your comment. The committee makes recommendations after considering all of the relevant evidence including expert advice. Section 4.3 has been amended to better reflect the possible benefits of avoiding paraesthesia mapping in the absence of published data.
87	20	Manufacturer	4.3	The clinical experts stated that paresthesia mapping may be distressing and disorientating for the patient.• Again, we can see no evidence that this statement is supported by any clinical evidence and suggest that the statement should be removed from the guidance.	Thank you for your comment. Please see the response to comment 82.
88	20	Manufacturer	4.3	"Furthermore, the experts advised that paresthesia awareness continues throughout the use of low frequency SCS devices, which may negatively affect day-to-day living."	Thank you for your comment. Please see the response to comments 82 and 86.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Again, this statement is not supported by clinical evidence. There are few, if any, data available on patient perspectives and preferences regarding paresthesia and their effect on quality of life, including driving and sleeping. Anecdotal patient and clinician reports of both negative and positive effects of paresthesia do not substitute for systematic data, and the absence of such data make it impossible to adequately evaluate the impact of paresthesia in spinal cord stimulation. It is unfortunate that this global assumption is given such prominence as we feel it fails to recognise that all patients are individual and their particular symptoms and circumstances will determine their view about what positively or negatively affects their day to day living.	
89	20	Manufacturer	4.3	However, the committee heard that some patients (usually those who have had SCS for a long time) find the paresthesia reassuring and a means of confirming for themselves that the device is still working.• We were pleased to see that the committee heard that paresthesia may have a positive impact in reassuring patients and consider that having a device offering both options for paresthesia and paresthesia-free stimulation is more effective in managing a patients satisfaction and preference.	Thank you for your comment.
90	20	Manufacturer	4.3	"The committee also noted significant potential quality of life benefits, such as patients being able to drive and use machinery while using Senza." We are concerned that this statement is potentially misleading as SENZA labeling does not contain an affirmative statement that 10 kHz patients may drive. Senza DFU states that 'it is less likely that sudden stimulation changes resulting in distraction could occur.• We believe that in order for the guidance to fully reflect the above statement, it should include the exact product DFU wording, which is significant given the importance of safety linked to the ability to drive. We also feel it is unfortunate that the committee did not consider the potential negative quality of life impact on patients with the Senza device, which includes the daily charging requirements, which may be intolerable for some patients. Primary cell SCS systems do not require charging and may be more appropriate or attractive to some certain patients. Furthermore, standard rechargeable systems typically require charging once per week, or less. The evidence shows that there is a three times higher charging burden to	Thank you for your comment. Please see the response to comments 63 and 85. Nevro provided a "10186-Rev.-J-Physician-Manual-(International)" as part of their evidence submission to NICE. This qualifies the Claim queried by this consultee: "Operation of Vehicles (e.g., driving) or Machinery - Patients using therapy that generates paresthesia (tingling sensations caused by stimulation) should not operate motorized vehicles such as automobiles or potentially dangerous machinery and equipment with the stimulation on when using paresthesia-causing programs. Stimulation must be turned off first in

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				maintain the results of HF 10 therapy as is needed to achieve equivalent pain relief (and sub-paresthesia) at 1,000 Hz (Thomson, 2017).We feel the guidance would be improved were the potential negative impact on a patients day-to-day life, which includes the patient having to manage his or her daily life around charging the device and the fact that this may affect a patients choice of device, be acknowledged.	such cases. For these patients, any sudden stimulation changes may distract patients from proper operation of the vehicle, machinery, or equipment. NevroTM SCS system's high frequency settings are designed not to generate paresthesia and its use does not restrict operation of moving vehicles."
91	20	Manufacturer	4.7	Considerations: However, because paresthesia mapping is not needed with Senza, procedure times are shorter and more predictable compared with those for low frequency SCS devices. We believe that this comment is unsubstantiated by data or clinical evidence and should be removed. As was acknowledged by the EAC the tariff payment for this procedure is identical regardless of the device used. If to be compared, procedural times should include all components of the total SCS lead implant procedure, and not only the very specific intra-operative step of using paresthesia mapping or not. Furthermore, the ability intraoperatively program is not restricted to the Senza device. There is evidence that low frequency SCS trials are performed without paresthesia mapping (Falowski et al., 2011). **SEE APPENDIX 1 FOR REFERENCES**	Thank you for your comment. The committee makes recommendations after considering all of the relevant evidence including expert advice. Section 4.7 has been amended to better reflect the possible benefits of avoiding paraesthesia mapping in the absence of published data. The EAC reviewed the Falowski et al. (2011) study and considered it out of scope as the device(s) were not specified, however the retrospective review of implants from 2002-2007 pre-dates 2010 CE marking of Nevro Senza. The outcomes reported are also for an awake versus asleep technique of device placement which the EAC considered not reflective of NHS practise.
92	20	Manufacturer	4.7	"The committee concluded that, even though this has had not been quantified in the cost-consequence modelling (see section 4.16), using Senza was likely to allow for better planning of procedures and potentially more procedures per day." We believe that this comment is unsubstantiated by data or clinical evidence.	Please see the response to comment number 91.
93	20	Manufacturer	4.9	"there may be further time savings at follow-up appointments, because programming SCS with Senza is easier and less time-consuming than programming low frequency SCS devices."	Thank you for your comment. The committee considered your comment carefully and decided to amend 4.8 to

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				We believe that this comment is unsubstantiated by data or clinical evidence and should be removed.	clarify that this statement was based on the experience of the clinical experts.
94	21	NHS Professional	-	One of the main advantages of the Senza technology is that the therapy is paresthesia free which is preferred by most patients. In the past paresthesia mapping at trial stimulation has been used as a marker to select patients for permanent implants; thus patients in whom stimulation provides paresthesia in the distribution of the pain are considered to have a positive trial and are therefore selected for a permanent implant (sections 4.3 and 4.7). This is because pain relief may not be obtained during the relatively short trial period (minutes to a maximum of one week) whilst paresthesia can occur immediately and so acts as a surrogate marker. Senza technology, however, is independent of this and therefore anatomical implantation is all that is required, removing the need for paresthesia mapping or indeed trial stimulation. Eliminating this step will further reduce the costs of this therapy, making it a single step rapid and efficient procedure.	Thank you for your comment.
95	28	Society	4.3	The document makes statements about reduced operating time and consequent cost savings using Senza, because of a lack of need for paraesthesia mapping. This is an assumed benefit which is not backed up with any data. Many practitioners using other systems do not routinely perform intraoperative paraesthesia mapping and so this consideration will often not apply.	Thank you for your comment. Please see the responses to comments number 85 and 91.
96	29	Manufacturer	2.4	Claim: No paresthesia so treatment can be continued during sleep and while driving or operating machinery. This claim seems to suggest that HF10 is uniquely able to deliver paraesthesia-free neurostimulation at the spinal cord. This is not true. Conventional low-frequency dorsal column stimulation elicits paraesthesia. BurstDR stimulation, like HF10, does not create sensation of paraesthesia in most patients as shown in Deer et al (Neuromodulation 2017). Additionally, dorsal root ganglion stimulation generates a lower level of paraesthesia, and may not be perceptible in many patients. In judging this claim, it will be important for the Institute to establish whether the DVLA has confirmed that patients receiving HF10 stimulation can drive and whether patients receiving conventional spinal cord stimulation cannot. Also, are patients receiving HF10 therapy granted motor vehicle insurance where patients receiving conventional spinal cord stimulation are not? If the DVLA and insurance requirements do not differentiate between the different types of technology, then guidance should not either. The MAUDE database should be checked for reports of paraesthesia and unwanted stimulation/shocks with HF10. If	Thank you for your comment. Please see the responses to comment number 90. Section 2.4 reflects the company's claimed benefits. The DVLA website lists notifiable health and medical conditions which should be reported to them: https://www.gov.uk/government/publications/g1-online-confidential-medical-information. This includes a category of “Spinal conditions, injuries or spinal surgery and driving”. The DVLA website states that decisions about any future driving restrictions are made on the basis of the individual patient report, in

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				such paraesthesia reports are found, the claim of no paraesthesia is invalid. The following MAUDE report numbers are relevant to the above statement: 3008514029-2017-00165 3008514029-2016-00089 3008514029-2015-00014 3008514029-2015-00004	consultation with their medical consultant, if necessary. The Nevro Physician Manual should inform the advice from medical consultant to DVLA, according to the individual patient's condition. The EAC found no evidence that the DVLA generalises its decisions on any driving license restrictions in the manner suggested by this consultee. The four MAUDE reports selected by the consultee were reviewed by the EAC and none relate to paraesthesias experienced by patients during driving. 3008514029-2017-00165 – Relates to a patient undergoing trial of the Senza system, who did not proceed to permanent implant. 3008514029-2016-00089 – Relates to a patient experiencing shocks at the IPG site during charging. 3008514029-2015-00014 - Relates to a patient experiencing shocks at the IPG site during charging. 3008514029-2015-00004 – Is a malfunction report for shocks at the IPG site and explant.
97	29	Manufacturer	2.4	Claim: No need for paraesthesia mapping during implantation, which allows shorter and more predictable procedure times. Whilst the point about paraesthesia mapping may be correct, conventional spinal cord stimulation generally requires one electrode to be implanted whereas HF10 requires two electrodes. So, procedure time may be shortened by the avoidance of paraesthesia mapping, but the time taken to implant the additional electrode, and cost of the additional electrode needs to be considered against this.	Thank you for your comment. Please see the responses to comment number 85. Section 2.4 reflects the company's claimed benefits.
98	31	NHS Professional	-	Also, many patients did not tolerate the parasthesia associated with low frequency stimulation- our experience with using both options for our patients was that it was a overwhelming preference for high frequency. Almost all patients undergoing a trial of both therapy selected the high	Thank you for your comment.

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				frequency stimulation. As a centre that has expensive experience in both high and low frequency stimulation it was very clear that high frequency was better tolerated. Patients who have failed to improve with high frequency generally do not improve with low frequency and we consider a failure of high frequency stimulation to be a failure of spinal cord stimulation in general. A number of patients do a lot of driving and 10kHz spinal cord stimulation can be continued to be use whereas low frequency stimulation must be switched off.	
99	35	Manufacturer	-	Other considerations Patient Impact It is important to note that all claims relating to paraesthesia free stimulation relate only to high frequency stimulation via the Senza device. It is unclear what percentage of patients are currently receiving conventional stimulation via the Senza device and therefore will not be receiving paraesthesia free stimulation. Important caveats to the claims in section 2.4 of the consultation document have been neglected. Claims related to paraesthesia seem to suggest that HF10 is uniquely able to deliver paraesthesia-free neurostimulation at the spinal cord. Conventional SCS elicits paraesthesia; however, all conventional stimulators are capable of delivering higher doses of energy, above or below perception threshold. We believe HF10 is not a distinct therapy different from SCS, but rather, it is a particular set of parameters that deliver a single dose of stimulation. Regarding claims for no need for paraesthesia mapping during implantation and treatment can be continued during sleep and while driving or operating machinery due to lack of paraesthesia. In both cases, these claims only apply when patients are receiving HF10 therapy; however, the Senza device is also capable of delivering conventional stimulation (defined as frequencies of 2 - 1,200 Hz), similar to all other market available SCS devices. According to the Senza Physician Implant Manual (11051 Rev A 2015-01-16), these claims cannot be made for patients using conventional stimulation with the Senza device. Importantly, if a patient is implanted with anatomical lead placement (at 10kHz and	Thank you for your comment. Please see the responses to comment numbers 96 and 97.

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				without paraesthesia mapping) and needs conventional settings, the leads may not be placed over the appropriate vertebral level in order obtain adequate paraesthesia coverage. Thus, an additional surgical procedure would then be required to modify lead placement. “Stimulation frequencies in the range of 2 Hz to 1,200 Hz are indicated for paresthesia-based therapy and the system must be configured to produce paresthesia. Stimulation at 10,000 Hz is indicated as paresthesia-free therapy and the system must be configured to deliver paresthesiafree stimulation. Stimulation between 1,200 Hz and 10,000 Hz has not been evaluated for safety, effectiveness and perception of paresthesia. Specifically, for stimulation frequencies above 1,200 Hz, amplitudes that produce paresthesias have not been evaluated and therefore it is unknown whether injury may occur.” “The safety of program settings above 1,200 Hz have not been studied above the T8 vertebral level.” “Patients using therapy that generates paresthesia (tingling sensations caused by stimulation) may choose to turn stimulation off to avoid uncomfortable sensations during sleep (see Warning regarding Stimulation Frequency). Therapy at 10 kHz does not generate paresthesia and therefore stimulation can remain on during sleep.” “Operation of Vehicles (e.g., driving) or Machinery – Patients using therapy that generates paresthesia (see Warning regarding Stimulation Frequencies) should not operate motorized vehicles such as automobiles or potentially dangerous machinery and equipment with the stimulation on. Stimulation must be turned off first in such cases. For these patients, any sudden stimulation changes may distract patients from proper operation of the vehicle, machinery, or equipment. Therapy at 10 kHz does not generate paresthesia and it is less likely that sudden stimulation changes resulting in distraction could occur while having stimulation on when operating moving vehicles, machinery, and equipment.”	

Characteristics of the technology: Other

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100	19	NHS Professional	-	7. Conclusions - I think EAC and MTAC need to re-consider. - Clinicians know and even Nevro admit to have treatment failures. Many of these are salvaged by alternative waveforms	Thank you for your comment.

Comparator

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101	19	NHS Professional		7. Conclusions - 10kHz SCS is also available from another manufacturer within Europe, although the manufacturer is not inclined to develop its product preferring to use the more energy efficient 1kHz waveform for its high rate SCS programme.	Thank you for your comment. Please see the response to comment 66.
102	32	Society		There have been advances in other technologies including Burst stimulation and DRG stimulation, but these were not used as comparator for the SENZA study.	Thank you for your comment. Please see the response to comment 66. The scope of this evaluation is described in the decision problem table. The comparator specified is low frequency spinal cord stimulation (up to 1200 Hz) which was chosen to represent standard care in the NHS. The MTEP process and methods guides describe the scoping process and choice of comparators for MTEP evaluations. The EAC considered any other spinal cord stimulation frequencies / modes / systems were out of scope of this evaluation.
103	20	Manufacturer	-	We welcome this draft guidance as a further demonstration that NICE continues to encourage the use of medical technologies for the benefit of patients and the NHS. We feel it is regrettable that more care was not taken in selecting truly representative comparative devices and feel that the evidence presented and evaluated, both scientific and economic, fell significantly short, which resulted in a sub-optimal draft consultation document.	Thank you for your comment. Please see response to comment 102.
104	6	NHS Professional	4.1	Based on expert advice, the committee considered that the low frequency non-rechargeable SCS devices are the most relevant comparator for use in the NHS. We believe based on data from the National Neuromodulation Registry Pilot as well as the advent of Burst Stimulation and other modes of higher charge stimulation, that this statement is erroneous and reflects only the practice of the clinical experts,. The appropriate comparator should therefore be rechargeable SCS conventional devices.	Thank you for your comment. Please see the response to comment 102. The committee received information about the National Neuromodulation Registry Pilot and considered it difficult to generalise the data to the NHS because of the small number of trusts involved in the pilot. The committee also received commercial in confidence information

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					from the NHS Supply Chain about the different devices used in the NHS. The committee considered the NHS Supply Chain data representative of NHS practice and decided to amend section 4.10.
105	15	Society	-	Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence? Economical evaluation has been done on the assumption of the HF10 Senza system with conventional low frequency SCS using either rechargeable or primary cell. This is probably not a correct reflection on current clinical practice in the UK. A pilot project which involved 5 implanting centres in the UK during the period of November 2014 to August 2015 (10 months), showed that the non-rechargeable system was 6% with Senza included and 9% without Senza. There has been a significant interest in new wave trains since HF10 was introduced into the market. Studies have shown other paraesthesia free wave trains to produce analgesia. Our data showed 28% of implants were low frequency SCS device and the rest capable of using other non-paraesthesia wave trains. ' Deer, T., Slavin, K. V., Amirdelfan, K., North, R. B., Burton, A. W., Yearwood, T. L., et al. (2017). Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation : Journal of the International Neuromodulation Society, 46, 489. http://doi.org/10.1111/ner.12698 ' Russo, M., Cousins, M. J., Brooker, C., Taylor, N., Boesel, T., Sullivan, R., et al. (2017). Effective Relief of Pain and Associated Symptoms With Closed-Loop Spinal Cord Stimulation System: Preliminary Results of the Avalon Study. Neuromodulation : Journal of the International Neuromodulation Society, 1569, 19. http://doi.org/10.1111/ner.12684 ' Wille, F., Breel, J. S., Bakker, E. W. P., & Hollmann, M. W. (2016). Altering Conventional to High Density Spinal Cord Stimulation: An Energy Dose-Response Relationship in Neuropathic Pain Therapy. Neuromodulation: Technology at the Neural Interface, 20(1), 71“80. http://doi.org/10.1111/ner.12529	Thank you for your comment. Please see the responses to comment numbers 102 and 104. The EAC reviewed the 3 studies outlined in your comment and considered them all out of scope (please see section 2 of the advisory document for further details. Deer et al. (2017) and Russo et al. (2017) were excluded on the basis Senza was not used. Wille et al. (2016) was excluded at the assessment report stage as the wrong population was used(failed conventional SCS and mixed CRPS and polyneuropathy).

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106	19	NHS Professional	2.1	In Europe, there are two manufacturers capable of providing 10kHz SCS - Nevro and Boston Scientific. Boston Scientific do not market their 10kHz product widely. Largely because of a disbelief in any claim to superiority of 10kHz over 1kHz that all current SCS devices are capable of. Reference Thomson S., Tavakkolizadeh M., Love-Jones S., Patel N, Gu W., Bains, A., Doan Q., Moffitt, M. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial " Neuromodulation 2018; 21.1: available on line ahead of print publication	Thank you for your comment. Please see the response to comment number 102.
107	19	NHS Professional	4.1	The national neuromodulation registry pilot revealed that more than 90% of low frequency SCS were rechargeable. Choosing a non-re-chargeable SCS comparator is incorrect and does not reflect UK practice. Since 2008 I have used only rechargeable SCS. I have not had to exchange one for battery end of life. Reference Thomson S., Kruglov D., Duarte R. A Spinal Cord Stimulation Service Review from a single centre using a single manufacturer over a 7.5 year follow up period. Neuromodulation 2017; 20: 589"599	Thank you for your comment. Please see the response to comment number 104. The EAC reviewed the Thomson et al (2017b) study and considered it out of scope as Senza was not used. Please see section 2 of the advisory document for further details.
108	20	Manufacturer	2.4	"clinically superior pain relief for most people with back or leg pain" Nevro claims that Senza is clinically superior for most people with back or leg pain compared to low frequency SCS. However, we encourage the committee to review Nevros official superiority labelling, which shows that superiority of 10 kHz only narrowly applies to the 13-year-old Precision Plus system used in the control group of the SENZA study. It does not apply to current SCS systems. The Summary of Safety and Effectiveness (SSED) issued by the United States Food and Drug Administration (FDA) outlined the control group to ONLY include Precision Plus in the SENZA study, saying 'superiority of the Test group over the Control group was demonstrated for the primary endpoint in the ITT, PP, and PS analyses.• (FDA SSED, page 45) Furthermore, the FDAs SSED casts doubt on the generalizability of the superiority finding in the SENZA study when it states 'although the data support the superiority of the Nevro device to the comparator, the comparator response rate was lower than that reported in the literature, i.e., 39% as compared to 80%. (FDA SSED, page 54)	Thank you for your comment. Section 2.4 reflects the company's claimed benefits.

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109	20	Manufacturer	4.1	The clinical experts explained that the low frequency SCS device used in the Senza-RCT is typical of those used in standard clinical practice in the NHS and that the available low frequency SCS devices do not differ significantly in terms of their performance. We are very concerned that this statement is simply one of hearsay and that there are no data or evidence presented to substantiate this claim. As such, this undermines the robustness of the guidance. The 'low frequency device• used in the Senza-RCT is Boston Scientifics Precision Plus, a 13-year-old spinal cord stimulation system that is several generations behind BSCs latest technology. Our internal data shows that the old system, Precision Plus, represents less than 2% of Boston Scientifics global implants, and has not been implanted in the UK in the second half of the 2017, to date. In the last ten years, technological advancements beyond frequency have been supported by clinical evidence and include improvements such as pulse train patterns (continuous vs burst), current delivery and lead contact polarity allocations (current vs voltage driven-stimulation, single- vs multiple source stimulation), and advanced programming algorithms (manual programming vs semi-automatic, based on 3D anatomic model). We would like to highlight to the committee the LUMINA study by Veizi et al., (2017), which is a large (n=426) multicentre, observational study demonstrating improved outcomes using modern SCS technology (Veizi et al., 2017). Again, we acknowledge that this evidence was not published during the initial stages of the Medical Technology Guidance process; however, we believe it is clinically relevant and, as such, should be considered in your evaluation. The study compared 213 consecutive Precision Spectra patients with a matched retrospective cohort of 213 consecutive Precision Plus patients (used in the SENZA RCT control arm). Results of the LUMINA study demonstrate that the new generation SCS system (Precision Spectra) achieved significantly better outcomes at 2 year follow-up than the older technology. For example, while the 2-year responder rate for low back pain was 41% in Precision Plus patients, it was 71% for Precision Spectra patients, i.e. >70% better ($p<0.001$). We would like to suggest that the inclusion and exclusion criteria for patients in the LUMINA study more accurately reflects SCS patients treated in actual clinical practice, including patients with only back pain,	Thank you for your comment. Please see the response to comment numbers 51 and 102. The EAC reviewed the Veizi et al. (2017) study cited in your comment and considered it out of scope as Senza was not used. Please see section 2 of the advisory document for further details.

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				mechanical spine instability, severely disabled with Oswestry Disability scores greater than 80 out of 100 and workers compensation (ESA/PIP) patients. All of these patients were excluded from the Senza-RCT. In summary, the LUMINA study provides real world clinical evidence that new technology provides better outcomes than the older SCS technology used in the control arm of the SENZA study. **SEE APPENDIX 1 FOR REFERENCES**	
110	20	Manufacturer	4.1	"Charging the device the low frequency non-rechargeable SCS devices are the most relevant comparator for use in the NHS." The consultation document, as currently drafted, is based on the Senza-RCT, which compares two rechargeable devices. We feel it is unclear why the committee would consider non-rechargeable devices as the most relevant comparator for use in the NHS. The most relevant comparator is rechargeable device programmed at a lower frequency and we feel this should be reflected in the guidance. This is important because unlike the Senza device, other currently available rechargeable devices offer a much lighter burden for the maintenance of the device operation. Instead of daily charging burden of 30 to 45 minutes as presented by the clinical experts, patients only have to recharge every week or every 2 weeks. In fact, the PROCO data concluded that a device set at 1 KHz was three times more efficient in charging than the 10 KHz device (Thomson, 2017). **SEE APPENDIX 1 FOR REFERENCES**	Thank you for your comment. Please see the response to comment numbers 63 and 104.
111	23	NHS Professional	4.1	I believe the main comparator should be rechargeable low-frequency versus HF10 based on a life span of 9 years or so. Though mapping during the procedure can take some time but can reduce the need for inserting the number of leads required from two to one commonly.	Thank you for your comment. Please see the response to comment number 104.
112	26	Manufacturer	-	Request that the results of both comparisons (HF10 therapy versus both TR and TNR) are presented for clarity and to align with the scope which determined Senza had to be compared to both alternatives. Whilst the therapy delivered is identical between TR and TNR, the device longevity (battery life) is very different and therefore had to be considered separately.	Thank you for your comment. Please see the response to comment number 104.

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113	28	Society	4.1	In its economic assessment the document states "Based on expert advice, the committee considered that the low frequency non-rechargeable SCS devices are the most relevant comparator for use in the NHS• . We strongly disagree. This is a misleading comparison because it conflates questions of possible benefits due to differences in stimulus pattern (low frequency versus Senza) with the economics of rechargability. In the long term, rechargeable systems are usually cheaper, because over their lifetime they generally save several battery replacements. The power consumption of the Senza system is such that a nonrechargeable system is impractical and thus it is only available in a rechargeable version. The fact that Senza is not available in a non-rechargeable version, which would be preferable to some patients, should be considered a potential disadvantage of Senza, not a justification for comparing the rechargeable Senza to a nonrechargeable low frequency device. The relevant economic comparison for Senza is with other rechargeable systems.	Thank you for your comment. Please see the response to comment number 104.
114	29	Manufacturer	1.1	Comparator. The inference is that low frequency spinal cord stimulation is the only other technology which is available to the NHS, which is not the case. Other forms of spinal cord stimulation have been introduced with the intention of improving pain control and reducing paraesthesia, often based on changes to the waveform produced by the implantable pulse generator. The commentary by Mogilner on the publication of the 24-month Senza RCT follow up confirms that conventional SCS or HF10 are not the only options available. The UK is predominantly a rechargeable market and Nevro currently has dominant market share.	Thank you for your comment. Please see the response to comment number 104.

Benefits of the technology

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115	12	NHS Professional	-	Using SENZA HF over the last 3 years we have seen significant improvements in comparison to traditional low frequency stimulation. The most notable are as follows: 1) reduced theatre time required for procedures 2) increased patient satisfaction due to the ability of patients to drive with the device turned on 3) more noticeable reduction in pain scores and improved functional scores when compared to other manufacturers/low frequency devices 4) ability to treat not only neuropathic leg pain but also address low back pain which most patients will have. The only real disadvantage to patients is the fact that they will have to charge the unit more frequently and may be unaware if the unit is not functional due to the lack of stimulation. The evidence for SENZA is increasing and of a higher quality than previous studies. Improvements in study outcomes do compare to what we are seeing in clinical practice using these devices.	Thank you for your comment.
116	14	NHS Professional	-	Our 6 year data of Senza HF10 therapy shows sustainability in pain relief over time of 50% or more. Improvement in sleep, QOL and functional outcomes have been demonstrated in our patients. Implantation time is less variable allowing better efficiency of theatre time. Patients being able to drive has significantly improved QOL Patients who drive for a living are now able to optimise their pain relief when driving. Patient feedback on charging and telemetry both demonstrate sustainability in charging time and battery capacity. Charging time of 30 - 45 minutes to full charge has been sustained over a 6 year period. Patient	Thank you for your comment.

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				feedback on charging daily or every few days does not appear to have been a burden.	
117	31	NHS Professional	-	I work as a consultant in pain management and have been using the high frequency spinal cord stimulation at 10kHz using the SENZA device for the 5 years as a consultant. It has been responsible for a major change in how we have been able to treat our patients with spinal cord stimulation. The most limiting factor was that in traditional low frequency stimulation, the axial lower back pain was poorly treated and spinal cord stimulation was restricted to patients with leg pain. Thus, many patients were excluded and few options became available. High frequency spinal cord stimulation at 10kHz allowed us to offer a therapy to treat both the low back and legs and increase our success rate of this therapy compared with traditional low frequency stimulation.	Thank you for your comment.
118	31	NHS Professional	-	Overall, the use of high frequency 10kHz spinal cord stimulation has been a highly significant change in how spinacl cord stimulation as a therapy can be delivered. It has allowed patients who have both axial low back and leg pain to be treated rather than only those with only leg pain. It increased tolerability and simplicity adds to its advantages.	Thank you for your comment.
119	16	NHS Professional	-	We have implanted about 120 High frequency SCS to date and we agree to the recommendations. There is strong level 1 evidence for its superiority over the conventional systems. The cost savings is additional factor. There will be however role for conventional systems and the newer waveforms that is being develops. There is also the miniature novel platforms that are being developed. But nonetheless, having experience in using these devices, it is undoubtedly superior to the conventional devices	Thank you for your comment.
120	31	NHS Professional	-	Another advantage in the high frequency device is that programming is simple and straightforward. Patients do not need to continually adjust any parameters and the device can be used continuously without interuption. Low frequency stimulation varies with posture and movement and often patients have to adjust the settings depending on their activities. Operating time is significantly reduced and use of this therapy has allowed us to increase theatre productivity as the intra-opearive testing can be omitted and this can save up to 30-45 minutes per case.	Thank you for your comment.
121	3	Patient	-	With regards to the consultation document with reference to HF10, I wanted to share my personal experience as a patient who received a trial and subsequent implantation of this system in February 2016.	Thank you for your comment.

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				Following a failed dynesis stabilisation surgery in 2004, I was given a spinal fusion at L4/L5 in 2008. I was left with sensory nerve damage in my legs, in particular my left leg, and was in severe pain. In 2010 I was given a low frequency spinal cord stimulator system to try and help with severe and debilitating pain in my lower back and legs. Following many months of testing new programmes I was never able to achieve any significant pain relief with the system and in fact it would often make my pain levels worse, not better. Even with 2 crutches, on a good day I was restricted to walking 30 metres but often I couldn't even manage this so whenever I left the house I was wheelchair bound. Often when my pain levels were really severe, I had to use my wheelchair in the house just to get from my bed to the bathroom. Many days a week I was almost confined to one room of the house and hardly ever went out. In 2016 I was offered a trial of the HF10 system at the John Radcliffe Hospital in Oxford. I had a strict regime of testing 3 different programmes at 3 different intensity levels over a 6 day period, and then I had 2 additional days to revisit any programmes I felt were benefiting me. Within 24 hours of being set up with the trial unit, I was feeling less pain in my legs and by 36 hours there was a marked improvement. On day 3 I noticed a very severe deterioration in pain levels and it turned out that one of my temporary leads had become disconnected and the unit had turned off. Within 6 hours of the system being reconnected the big improvement in pain levels continued. In addition to the pain relief, by day 4 I was walking the length of the ward with no crutches, and by day 6 I was walking the entire length of the department without any walking aids and was continuing to see a big improvement in pain levels. This was sufficient evidence to allow me to be given the HF10 system permanently. The decision was taken that they would piggy back the existing wiring and electrodes from my original stimulator system but replace the battery unit with the HF10 rechargeable unit. When I got home, I continued to carefully test each programme I was given for several days, and kept a detailed spreadsheet to record exactly what effect each test programme was having on my back pain and leg pain. Over the following months I tested several different programmes and finally settled on 2 programmes which gave me the most benefit.	

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122	3	Patient	-	Before I was given the the HF10 system, my average leg pain score was 8/10 and back pain was 7/10. Now, my leg pain is down to 2 or 3/10 and my back pain is at 4 or 5/10 depending on my activity levels. On a good day I can walk up to half a mile with 1 stick to support my weak leg. I have been able to reduce the dose of my optiate pain medication by more than a third and am continuing to try and reduce this further. I take less anti-nausea medication and am currently working on reducing my antidepressant medication. The biggest effect on my quality of life has been with regards to sleeping. Before I was given the HF10 system, I would only sleep 3 hours a night, often broken every half an hour because of pain; I was constantly exhausted. I regularly needed to visit my GP for a temporary course of sleeping tablets. 4 nights a week now I will sleep for 7 or 8 hours, often with only one wake up to adjust my position before falling back asleep again. I no longer require sleeping tablets. Getting decent quality sleep due to a reduction in pain levels has had a massive positive effect on my mood and mental health state. I am now able to live a much better quality of life. Because of the improvement in my mobility I am able to get out more, have been making slow but steady progress with regards to starting to get back to work again. It is difficult to put into words just what a positive effect this system has had on my quality of life - my husband and I often tell people it has been miraculous. I hope that my experience will be taken into consideration during the consultation. I'm sure there are many more people out there who could benefit from this technology, and ultimately save the NHS money by taking less pain medication and needing fewer hospital appointments.	Thank you for your comment.
123	7	Patient	-	I was involved in a road traffic accident in 2012 in which i sustained a spinal cord injury, after various neuropathy interventions the decision was made to trial the spinal stimulator. The trial went really well and i was put forward to have a permanent stimulator implanted. The day of the surgery arrived and all went all, despite the obvious pains from the surgery i felt good.	Thank you for your comment.

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				As time went on things just got better and better and i found myself able to do things that i hadn't been able to do since the accident, i now feel like i could not live without my implant and the pain relief it gives me, it has changed my life.	
124	10	Patient	-	I had the Nevro, senza High frequency spinal cord stimulator implanted in 2012 as part of a trial programme at St. Thomas hospital, London. It has, with out a doubt, changed my life since I had the non invasive procedure, that I am now back to work and able to swim again. The 'gizmo' is easy to use by use of a remote control to change the ampage out put to help with pain relief and the daily charging of the unit is something that can be done in the evening when relaxing. This device has changed my life no end, as I am off benefits and now doing a job I love. My family life is brilliant as I can now be a Dad to my children and a Husband to my wife. The money saved by me having the implant easily outweighs the savings made by coming of benefits and starting to pay tax. The reduced visits to see my GP and prescriptions is also a massive saving. For me, the HF10 is something that the NHS should be supporting as the overall cost savings, I believe, would far out weigh the cost of the device and the theatre costs of implanting.	Thank you for your comment.
125	11	Patient	-	I have a Nevro HF implant - inserted in April 2016. The reason for implant was to control neuropathic pain in my neck which had not been controlled by other therapies. Since the implant, my pain medication was rapidly eliminated and I have negligible remaining pain issues. I have been able to build up my sporting activity and hope soon to return to levels achieved prior to the injury that caused the pain problems. Although implanted from C2, I am pursuing competitive horse riding without issue whilst using the Nevro, just ensuring I wear air-jacket protection to protect the implant in falls (the implant has survived one fall so far). I hope that use in sports men and women will be developed further in future as well as use in less active patients as the quality of life benefits are considerable. I have found not only the therapeutic effects but also the post implant support from Nevro representatives exceptionally effective.	Thank you for your comment.

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126	13	Patient	-	I have suffered from back and leg pain for the past 16+ years. I have undergone 2 Spinal fusions, the first with better success than the second. I then suffered from inflammation of the facet joints around the area of fusions. This led to numerous steroid injections which, eventually, failed to provide relief. I was referred to Dr Muldoon for pain relief advice before my surgeon would consider a third Spinal Fusion. In January 2017 I underwent a trial for Senza Spinal Cord Stimulator with excellent results leading to permanent implant in May 2017. My life has been totally turned around. I'm now 90% better pain wise with only occasional back pain, nothing more than someone without Spinal problems would experience. I have no leg pain at all. I can honestly say this has changed my life. I'm now sleeping better, pain medication has reduced and hopefully will not be needed as the system beds in more. Could I run a marathon? No - but I can now stand for longer and walk a bit further without pain. Simple daily tasks which caused me considerable pain in the past are now so much easier. I'm still in the early stages of having this system so I'm looking forward to the future.	Thank you for your comment.
127	17	Patient	-	Following a failed discectomy at L4/5 for back and leg/foot pain in 1996 I was finally implanted with a Nevro Spinal Cord Stimulator in 2015. I no longer need to take Tramadol/Pregabalin for pain relief as I am pain free with daily inductance charge of my stimulator at home. The system fulfils its promised function.	Thank you for your comment.
128	22	Patient	-	As patient suffering from FBSS having had chronic leg pain for nearly 9 years I am thrilled with my Nevro implant. I found the surgery to be the hardest part,especially being awake for the implantation of the leads, but since recovery I haven't looked back. I like the fact I can't feel the sensation of it working & that it can remain on all the time. I would find it distressing to have to turn it off to drive or sleep & be in pain during those times. I have developed a routine for charging & it has become a habit not a chore. I am now 95% pain free for the first time in 9 years and as a result I have started my own business dog walking (amazing as 9 years ago I thought I'd never walk again) since surgery just over a year ago my business has doubled & there is no stopping me. I am also completely off all other pain medication. This device has given me back my life.	Thank you for your comment.
129	25	Patient	-	I note that the consultation document suggests those with failed back surgery are prime candidates. I was in that class, but also in the class where nerve compression had caused permanent nerve damage creating the neuropathies of sensory, motor and pain. I note the point about charging, and would confirm that with a good	Thank you for your comment.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				pattern, and a similar charging time each night, it is not so intrusive. I did though find when the pattern was interrupted due to wife's illness, charging became more of an issue. In term of efficacy, I noted an immediate relief of neuropathic pain in my right leg on the trial, with the ability to stand for longer than I had, before the pain increased. I walked out of hospital pain free for the first time in three years. Having had the implant in place for 360 days, efficacy has been maintained in the long term, which has allowed me to reduce tramadol from 200mg SD bd - 150mg SD bd, and Pregabalin from 150mg qds to 150 mg bd, along with a total reduction of oramorph at 20mg/30mg nocte. Sleep has improved, along with sitting time and standing time. Pain relief levels have been maintained whilst the dosage decreases have occurred. Therefore the implant was able to initially 'treat' 25-30% of the pain not covered by drugs, but then also allow considerable drops in pain relief drugs, whilst still maintaining the base line pain relief level noted on trial implant and full implant. Pain relief is at a level of about 1-2, with a level mostly at a relative level of 1. I know there is some discomfort there, but it is more an itch than a fundamental lifestyle issue, as it had been. The important point missed, is that the implant also allows for opioid drug reduction, which is key, as I am suffering from pituitary poisoning caused by the tramadol. In terms of side effects, all that I can find seem to be caused by the ability to walk more, which has caused an ulcer on the foot with the neuropathy. It appears that the motor neuropathy and associated palsy causes an erroneous foot position, which has given rise to the ulcer. I can confirm that I have not encountered any side effects associated with this pain relief mechanism. In conclusion, the implant was able to provide much needed top up in pain relief to improve physical activities greatly, but then allowed a drop in pain relief medication which was also substantial, with a drop of 50% reduction in pregabalin, along with a further 50% + reduction in opioid dose equivalency.	

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
130	1	Society	-	On behalf of the Spine Intervention Society (SIS), I would like to commend the National Institute for Health and Care Excellence (NICE) on the draft medical technology assessment of Senza's High Frequency 10kHz Spinal Cord Stimulation (HF10 SCS) to treat chronic neuropathic pain. Traditional SCS is a well-established treatment for patients with refractory chronic neuropathic pain. More recently, HF10 SCS therapy has demonstrated benefits that exceed even those of traditional SCS. The NICE assessment appropriately identifies and summarizes the evidence demonstrating the safety and effectiveness of HF10 SCS therapy and concludes that it represents an advancement in SCS programming and technology that has demonstrated superiority in controlled studies to traditional SCS, an already well-established and covered treatment. SIS supports the recommendation that HF10 SCS therapy be a covered treatment for patients with chronic neuropathic pain.	Thank you for your comment.
131	9	Private Sector Professional	-	I have been very impressed with the HF10 Nevro spinal cord stimulator and Nevro as a company. Nevro have undertaken a lot of scientific research into the mechanisms of action of HF10. This has translated into a spinal cord stimulation system that has, in my opinion, exceptional results in terms of reduction in pain scores and high levels of patient satisfaction. In the series of patients I have implanted with Nevro HF10 I have not experienced any adverse consequences.	Thank you for your comment.
132	21	NHS Professional	-	The NICE appraisal of the Senza technology for delivering high frequency spinal cord stimulation to treat chronic neuropathic pain represents a first of its kind and is welcome in the field of functional neurosurgery and pain management. As new technologies evolve, we hope that similar timely appraisals promote rapid adoption within the NHS for the benefit of patients. We are particularly encouraged by the economic analysis, showing clear advantage over best medical therapy in patients with intractable chronic pain.	Thank you for your comment.
133	23	NHS Professional	-	Overall, I support that HF10 (and perhaps all other rechargeable SCS systems able to deliver higher energy levels) should be included in TA159 and routinely be available to patients as an option and routinely funded by CCGs. The evidence suggests advantages for each treatment modality but for	Thank you for your comment.

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				the FBSS patients with predominant neuropathic back pain (rather than buttock/leg pain) HF10 seems more promising and should carefully be considered after thorough multidisciplinary assessment.	

Patient choice and equality

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
134	19	NHS Professional	-	7. Conclusions - I think EAC and MTAC need to re-consider. - Patients and Clinicians want choice. They do not want to be told erroneously that this product is superior when it is not. - Products that allow flexibility is the future, not a one mode for all approach. No other field of medicine would suggest something as complex as this only requires one type of treatment. I welcome Nevro HF10kHz as an alternative manufacturer of SCS with a single, initially novel, waveform, however it is unsafe to give superiority status to this product.	Thank you for your comment. NICE medical technologies guidance evaluates a single medical technology based on the claimed advantages of introducing the specific technology compared with current management of the condition. It is not a multiple technology assessment and does not compare evidence for all similar technologies in a broader class. These principles are described in further detail in the Medical Technologies Evaluation Programme methods guide, and in the block of text at the beginning of the medical technology guidance. This text states that the case for adoption is based on claimed advantages of introducing the specific technology compared with current management of the condition. It also states that the specific recommendations in the medical technologies guidance on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages.
135	32	Society	-	Most of the neuromodulators in the UK are concerned about NICE recommending that this therapy is better than others as this may limit choice for patients and physicians if we are limited to one therapy.	Thank you for your comment. Please see the response to comment number 134.
136	2	Patient	-	This is not a one size fits all. From a patient point of view there should be choice.	Thank you for your comment. Please see the response to comment number 134.
137	8	NHS Professional	-	At NBT we feel that Spinal Cord Stimulation devices should not be restricted to one of the 5 companies that make them. Each device has different technology (frequency, position) which enables choice and best treatment for patients (all at approximately equal cost). We hope that this guideline will not restrict choice.	Thank you for your comment. Please see the response to comment number 134.
138	30	NHS Professional	-	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any	Thank you for your comment. One of the main aims of medical technology

				group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? It should be considered that patients in different geographical areas may not have the advantage of treatment provided by the Senza stimulator when assessed by clinical teams unfamiliar with the system. There may therefore be geographical discrimination in access to treatment. These clinical teams should refer patients for assessment and treatment in different clinical teams with expertise with the Senza simulator should the patient wish to consider this option.	guidance production is to promote faster uptake of new medical technologies guidance in the health and social care system.
139	35	Manufacturer	-	Other considerations Are there any equality issues that need special consideration and are not covered in the medical technology consultation document? No	Thank you for your comment.

Cost Model

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
140	4	NHS Professional	-	Whilst the warranty on the Senza battery is 10 years. The patient charger and accessories only has a 12 month warranty. These regularly break around 12-18 months and require replacement at additional cost.	Thank you for your response. The EAC concluded that it is not common practice to incorporate failure of device accessories into the economic models unless this would directly affect the patient (e.g. complications of implanted device). It would be possible to do this by changing the value of the base case; however, this should be done on the basis of evidence rather than anecdote, and evidence would also be required for the comparator, which the EAC has not been able to identify. Issues concerning battery charging and battery life are discussed in the advisory document in Section 6.1.
141	29	Manufacturer	1.3	Reliability of section 1.3. What is the cost of rechargers for conventional and HF10 devices and have these been taken into account? As rechargers have a finite lifespan determined by their usage, and that rechargers used with the HF10 battery are used up to 14 times more frequently than rechargers for conventional devices, is there a difference in length of service and replacement frequency? For example, what number of rechargers are issued per pulse generator? It would be reasonable diligence for the institute should check how many Senza devices were issued in the UK compared to HES data of the same time period. If there are differences, this needs to be factored into the economic considerations. This could also place a burden on NHS services in that there could be a substantial activity needed to re-order and re-issue replacement rechargers to patients.	Thank you for your comment. Please see the responses to comment numbers 63 and 140. It is not possible to identify specific devices through HES data.
142	20	Manufacturer	1.3	“savings are mainly from Senzas longer lifespan and few associated complications” We are concerned that the draft guidance appears not to have recognised that the statement above is one of the 'claimed benefits• presented by Nevro rather than a statement supported by the evidence. For example, in Nevros model the optimal or suboptimal pain relief with complications assumed zero probabilities at both baseline and in the sensitivity analyses. We feel this is important	Thank you for your comment. Please see the responses to comment numbers 141 and 143. The base case model did not assume zero probability for complications associated with Senza for any of the clinical states.

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				because whilst the model blinded the complications from the Senza-RCT, Kapural et al. reported patients implanted with HF10 did experience adverse events, including implant site pain as well as lead migration. Therefore, assuming zero probabilities for pain relief with complications is not accurate and diminishes the robustness of the model. We respectfully request that the committee reconsiders making this statement.	
143	35	Manufacturer	-	Model inputs Explant rates The 1 and 2-year explant rates in the model are from Nevro data on file and are not available for comment. At year 3, the model uses a 3.2% explant rate based on Taylor et al (2010) (8), which may be considered outdated. We suggest that the explant rates from more current sources are tested in the model. In a recent multicentre study, Van Buyten et al (4) undertook a multinational chart review of 955 patients to determine if there were any differences in the rate of explant for the different types of SCS in use today. They reported a rate of explants for inadequate pain relief of 6.9% per year for non-rechargeable SCS, 11.2% for conventional rechargeable SCS and 14.2% for HF10 stimulation. This large study provides an estimate for real-world explant rates and also addresses long-term efficacy in the form of explants related to lack of efficacy. We believe it would be appropriate to examine these recent real-world data in the economic model as explantation rates are stated as an important cost driver by the EAC. (Page 64 of EAC report – "explantation was a key driver of the model because patients who have devices explanted moved to the CMM side of the Markov model"). **SEE APPENDIX 2 FOR REFERENCES**	Thank you for your comment. Please see the response to comment number 4. The EAC advised the committee that major complication rates (requiring explantation) is one of the key drivers of the model. This has been explored using data from the recent Van Buyten et al. (2017) study in in Section 7.2.2 of the EAC advisory document. On consideration of this new evidence the committee decided to amend section 1.3. This change was also reflected in revisions to section 3 and 4 of the guidance.
144	35	Manufacturer	-	Model inputs Complication rates "The EAC considers that the handling of the complications in the model structure was not transparent in the original publication (Simpson et al 2008) (9) (External assessment page.) The data on complications has been redacted in the EAC report. The rational for the treatment of patient safety data as "commercial in	Thank you for your comment. Please responses to comments 1 and 143. The redacted complication data was academic in confidence, as the company plan to publish this data at a later date. The EAC advised that the model is insensitive to changes in the minor complication rate. The De Andres study reported on low patient numbers. The

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				confidence" is unclear. As the complication rates have been redacted we cannot see what complication rates have been used in the model and are unable to review the impact of the chosen rates on the outputs of the model. We suggest that complication rates are taken from published data sources and that commercial in confidence data should not be used to inform decision making. In the recent paper by De Andres et al. (2) they state that "The most common AE was lead migration, which was significantly more frequent in the HF group during the trial period and required surgical revision at the same time as the IPG implant (P<0.05)". The higher rate of lead migration may influence the overall costs with HF10 and we suggest that these rates and other published data on complication rates should be tested in the economic model. **SEE APPENDIX 2 FOR REFERENCES**	EAC does not consider lead migration during the trial would have significant cost impacts.
145	19	NHS Professional	1.3	The cost-effectiveness rationale of HF10 SCS is based on a single low-quality publication (Annemans et al.). It is noted in the report that the Nevro system alone costs £16,648 (excluding VAT), and yet the model from Annemans et al. assumed a cost of £15,056 for the Nevro system and entire HF10 implant procedure, and used cost data provided by Nevro. The paper described initial state probabilities in table 1 but did not consider, or used without explanation, any probability of state transition between optimal and suboptimal pain relief. It also made a rationale for identical complication rates with HF10 and conventional SCS based on limited evidence. To achieve credibility, a cost-effectiveness analysis needs to be based on conservative, widely accepted assumptions. This was not the case for the single publication that was considered. The appropriate comparator is NOT a non-rechargeable device but rather a parasthesia based rechargeable device. The pilot of the UK National Neuromodulation showed that more than 90% of non-HF10kHz SCS were rechargeable SCS devices. Furthermore a UK series over 7.5 years by Thomson et al 2017(26) is a series of 321 patients treated with SCS at one institution with parasthesia based (traditional) rechargeable devices. Not one implantable pulse generator	Thank you for your comment. Please see the response to comment number 1, 104 and 143. The model used in the sponsor's submission was a de novo model, structurally based on the model used to inform TA159. A full description of the model, its assumptions, and the EAC's assessment of these assumptions is documented in the company submission and EAC's assessment report. Many assumptions were considered to be conservative by the EAC and the EAC was satisfied with the sensitivity analysis performed. The EAC has addressed concerns concerning Senza II in Section 7.2.5 of the advisory document. Following advice from the EAC and the company the

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				was replaced because the IPG had become end of life. In this series baseline and follow-up utility data was collected. On average and over a 15 year time horizon, 6.9 QALY per patient were gained. This is Real world data from patients treated in line with NICE TA159 (26). Finally, I understand that Nevro will soon be launching Senza 2 now that it has a CE mark. This is priced at a premium rate. It is likely that implanters of Nevro Senza will quickly change to Senza 2 with NHSE paying a premium price since many of the first generation glitches and smaller size maybe attractive concepts. If the Medical Technology Advisory Committee gives special status to Nevro Senza, the reality of the cost effective analysis will be even further away from the economic model presented. These are from Nevros Chief Finance Officer, Andrew Galligan, in a recent earnings call on 6th November 2017. 'So, fundamentally as volumes grow, we have been able to get cheaper product pricing, is the fundamental move, response that we had this quarter. The new product has both positives and negatives. It's a new product, so initially it's a little bit more expensive and over time it will go down in cost. But as against that, it will be premium priced. So, one hopes that over time it will have a positive impact on margins. Reference 26 Thomson S., Kruglov D., Duarte R. A Spinal Cord Stimulation Service Review from a single centre using a single manufacturer over a 7.5 year follow up period. Neuromodulation 2017; 20: 589“599	committee decided to amend the guidance to acknowledge this device, however it is not part of this evaluation. Please see section 2.4 of the MTG.
146	19	NHS Professional	3.5	There are flaws in the economic model of Annemans. The actual costs of the unit are incomplete The typical UK comparator is rechargeable SCS. The new Senza 2 is deliberately premium priced ready to capitalise upon a favourable MTAC reportThe cost-effectiveness rationale of HF10 SCS is based on a single low-quality publication (Annemans et al.). It is noted in the report that the Nevro system alone costs	Thank you for your comment. Please see the response to comment number 145.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Â£16,648 (excluding VAT), and yet the model from Annemans et al. assumed a cost of Â£15,056 for the Nevro system and entire HF10 implant procedure, and used cost data provided by Nevro. The paper described initial state probabilities in table 1 but did not consider, or used without explanation, any probability of state transition between optimal and suboptimal pain relief. It also made a rationale for identical complication rates with HF10 and conventional SCS based on limited evidence. To achieve credibility, a cost-effectiveness analysis needs to be based on conservative, widely accepted assumptions. This was not the case for the single publication that was considered. The appropriate comparator is NOT a non-rechargeable device but rather a parasthesia based rechargeable device. The pilot of the UK National Neuromodulation showed that more than 90% of non-HF10kHz SCS were rechargeable SCS devices. Furthermore a UK series over 7.5 years by Thomson et al 2017(26) is a series of 321 patients treated with SCS at one institution with parasthesia based (traditional) rechargeable devices. Not one implantable pulse generator was replaced because the IPG had become end of life. In this series baseline and follow-up utility data was collected. On average and over a 15 year time horizon, 6.9 QALY per patient were gained. This is Real world data from patients treated in line with NICE TA159 (26). Finally, I understand that Nevro will soon be launching Senza 2 now that it has a CE mark. This is priced at a premium rate. It is likely that implanters of Nevro Senza will quickly change to Senza 2 with NHSE paying a premium price since many of the first generation glitches and smaller size maybe attractive concepts. If the Medical Technology Advisory Committee gives special status to Nevro Senza, the reality of the cost effective analysis will be even further away from the economic model presented. These are from Nevros Chief Finance Officer, Andrew Galligan, in a recent earnings call on 6th November 2017. 'So, fundamentally as volumes grow, we have been able to get cheaper product pricing, is the fundamental move, response that we had this quarter. The new product has both positives and negatives. It's a new product, so initially it's a little bit more expensive and over time it will go down in cost. But as against that, it will be premium	

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				priced. So, one hopes that over time it will have a positive impact on margins.• Reference 26 Thomson S., Kruglov D., Duarte R. A Spinal Cord Stimulation Service Review from a single centre using a single manufacturer over a 7.5 year follow up period. Neuromodulation 2017; 20: 589“599	
147	20	Manufacturer	3.5	“The EAC was satisfied that the models structure, assumptions and parameters were robust and accurately reflected the important considerations.” After a thorough review of the cost consequence model submitted by Nevro, we feel there are a number of issues that diminish the robustness of the model in both its accuracy and the results. We have listed these below. 1. Constant mortality rate assumption in a 15-year model In Nevros model, it appears the annual mortality rate was fixed at 0.81% for all patients and the sensitivity analysis was very narrow - ranging from 0.73% to 0.89%. However, as patients age, their background mortality rate increases accordingly, independent from disease-specific mortality rate. For instance, the UK National Life Table 2015 (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/previousReleases) indicates that a 50-year-old male has a background mortality rate around 0.34%. Assuming this patient survives in a 15-year model, at age 65, his mortality rate would increase to 1.21%, hence, a 256% increase in mortality risk in 15 years. If disease-specific mortality risk was considered on top of the background mortality risk, then the risk of patient dying over the course of 15 years would be even greater. Depending on the starting age of the intervention groups, the different mortality risks of the patient group would affect the cost outcomes. Ideally, we feel the model would have been strengthened by use of a dynamic mortality risk factor which incorporated should be considered by incorporating both background and disease-specific mortality risks. 2. Probability assumptions on complications	Thank you for your comment. Please see the response to comment number 142 and 145. The reviewed your comment regarding mortality rates and concluded that the mortality rate used is a crude average of life expectancy in people aged 0 to 100 years. As the underlying conditions causing back and leg pain are assumed to be unrelated to life expectancy, and none of the interventions included are curative, the mortality rate used does not meaningfully impact on the model, as it is the same for all technologies. Additionally, a starting age does not have to be assumed.

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				In Nevros model the optimal or suboptimal pain relief with complications assumed zero probabilities at both baseline and in the sensitivity analyses. While the model blinded the complications from the Senza-RCT, Kapural et al. reported patients implanted with HF 10 did experience adverse events, including implant site pain as well as lead migration. We believe therefore that, assuming zero probabilities for pain relief with complications is not inaccurate and diminishes the robustness of the model. 3. In general, we strongly believe it is important to assess the trade-off values in economic evaluations The model built by Nevro, following the NICE TA-159 template, was a cost-consequence model rather than a cost-utility model. In general, we feel that by not assessing the trade-off perspective of the cost (e.g., different effectiveness or benefits, including QALY gained) this only constitutes a partial economic evaluation as it does not relate costs to benefits. We feel it is unfortunate that this approach was used as the use of partial evaluations are useful only to provide elements of information, but they do not provide all the FULL information necessary for cooperative decision-making. We would urge the committee to reconsider the strength of the economic evaluation.	
148	20	Manufacturer	3.6	“The EAC considered the companys cost model to be of good methodological quality and was satisfied with the reported results and sensitivity analysis” Annemans et al. (2014) conducted cost-utility analyses (CUA) comparing non-rechargeable, rechargeable and HF10, with that of CMM and reoperation over the course of 15 years (Annemans, Van Buyten, Smith, & Al-Kaisy, 2014). Based on the findings from the 2-stage economic model, compared with CMM, the incremental cost-effectiveness ratios (ICERs) for all 3 SCS comparators (non-rechargeable, rechargeable and HF10) were well below the commonly accepted willingness-to-pay (WTP) threshold of Â£20,000 in UK (Â£8,802, Â£5,101 and, £3,153, respectively). Compared with reoperation, the ICERs were: £11,864, £4,849 and, £2,666, respectively, also well below the WTP thresholds. Hence, all 3 SCS treatments were considered cost effective treatment options compared with CMM and reoperation. When different SCS treatments were compared amongst themselves, Annemans et al. (2014) reported that HF10 was associated with lower cost and higher QALY gained over the	Thank you for your comment. Please see the response to comment number 145. The company provided break even analysis on when Senza HF10 was predicted to become cost-saving. This was immediate compared to rechargeable SCS, and about 4.0 years compared non-rechargeable SCS (Figure 32 of company submission).

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				course of 15 years. We feel it is unfortunate that there is no clarity about the length of time it will take for payers to recuperate their costs and reach a 'break-even point' based on Annemans et al. (2014). Given that all SCS were found to be cost-effective compared with CMM and reoperation, we feel that simply stating 'Senza was the most cost-effective treatment, dominating both rechargeable and non-rechargeable low frequency SCS devices' presents incomplete information and would urge that the draft guidance is modified to reflect this situation. In addition, we feel the guidance would be better balanced if it acknowledged the time it takes to reach the stated results (15 years) and that all SCS treatments had a WTP lower than £20,000. **SEE APPENDIX 1 FOR REFERENCES**	
149	20	Manufacturer	3.7	The EAC considered the companys cost model to be of good methodological quality and was satisfied with the reported results and sensitivity analysis• As stated above in comments related to section 3.5, after a thorough review of the cost consequence model submitted by Nevro, we believe there are have identified a number of issues that diminish the robustness of the model and accuracy of the results including the assumption of a constant mortality rate as well as a zero-probability assumption on complication rates. We respectfully request that the wording be amended to reflect the uncertainty and diminished robustness highlighted.	Thank you for your comment. Please see the response to comment number 147.
150	20	Manufacturer	3.9	The main drivers of cost savings were device longevity particularly for non-rechargeable SCS devices, which must be replaced every 4 years and complication rates." As raised in our first comment, we do not feel it is valid to compare rechargeable SCS with non-rechargeable as rechargeable devices will naturally lead to longer device longevity and the greater cost savings associated with avoidance of battery replacement every 4 years. We feel it would improve the guidance if it were to acknowledge that there is currently no evidence to prove that Nevros HF 10 rechargeable device has greater longevity than other SCS rechargeable devices on the market. Furthermore, in addition to Nevro, every other SCS manufacturer in the United Kingdom offers a rechargeable device as	Thank you for your comment. Please see the responses to comment numbers 143 and 145.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				well as a non-rechargeable device. So, Nevro is not significantly differentiated in cost-savings from other devices currently on the market. We also feel the guidance would be strengthened if it provided clearer information about adverse events and complication rates. While the company highlighted that some of these were 'academic in confidence,• we would like to suggest that the document acknowledge the EACs concerns regarding the lack of transparency around these issues and that the data provided to the EAC by the company was found to be incomplete. We are concerned that by not including this information the guidance could be perceived as not presenting a true picture of the scale of potential complications associated with this device.	
151	20	Manufacturer	4.11	We note that the committee concluded that the use of Senza is 'likely' to be cost saving, however the EAC highlighted that uncertainty existed and was compounded by the fact that the model had a 15-year time horizon, which was considerably longer than the follow up of the clinical trial this guidance is based on. We feel there are a number of important factors that have not been highlighted in the report and that their exclusion potentially undermines its robustness. We respectfully request that these concerns raised by the EAC should be acknowledged in the guidance.	Thank you for your comment.
152	29	Manufacturer	1.3	Reliability of section 1.3. It is noted that the EAC used a Senza system cost of £16,648 (excluding VAT), and yet the model from Annemans et al used a cost of £15,056 for the Senza system and entire HF10 implant procedure. Annemans et al described initial state probabilities but were not explicit as to what transition probabilities were used to reflect movement between optimal and sub-optimal pain relief. Annemans et al also used identical complication rates with HF10 and conventional SCS based, which the explant data from van Buyten et al (2017) show is not the case in real-world experience. The Annemans paper is therefore unreliable as a source of evidence. A cost analysis needs to be based on determination of the correct inputs for each alternative therapy. Where differences in event rates between alternatives are known, they should be used.	Thank you for your comment. Please see the response to comment number 142, 143 and 145. With regards to your comment on Annemans et al. (2014), the EAC confirmed there was no movement between optimal and sub-optimal pain relief in the model, nor any value attached to these states.
153	29	Manufacturer	1.3	Reliability of section 1.3. Credibility is ascribed to the companys economic submission by assertion that was based on the published Annemans study and that the model was also used to inform NICE	Thank you for your comment. Please see the response to comment number 143 and 145.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				technology appraisal guidance on spinal cord stimulation. However, Annemans et al note that Since the model does not entirely match the follow-up data, we performed a scenario analysis whereby the model was calibrated to exactly match these follow-up data for HF10 SCS therapy• . In other words, an undefined correction was applied to make the economic model fit the data. An undefined correction is not a basis for using this publication as a reliable source of evidence .	The EAC is not clear what this "undefined correction" is and further clarifications have not made it clearer. The EAC has carried out validation of the model structure. For example, the timelines are consistent with those used in TA159, with a 15 year time horizon used. The EAC has also independently replicated the model using R code and is satisfied it works as described. As has been documented, there is some uncertainty regarding model inputs,
154	32	Society	-	The MTEP document states that the introduction of high frequency stimulation is unlikely to change the indications of treatment compared to traditional spinal cord stimulation, thus conferring an overall cost-benefit to the NHS. In the SENZA study, there are good outcomes on treating leg pain and back pain in FBSS. There may be positive evidence in the future for treatment of back pain alone in patients who have not had surgery at all. This would potentially increase the referral base quite dramatically and it should be recognised that we will probably implant more patients if evidence about HF stimulation is implemented, thus increasing the over-all costs as compared to current practice.	Thank you for your comment.
155	35	Manufacturer	-	Other considerations Healthcare Resource Use In the scope document the Committee concluded that "Senza SCS may offer benefits to the healthcare system through a reduction in operative time resulting from the avoidance of intra-operative mapping. This may enable costs savings through an increase in the number of patients treated on surgical lists". It should be noted that in a variation to the scope, the sponsor omitted the outcomes related to implantation time in theatre, follow up appointments and staff conducting device programming, as they did not identify any objective data from published trials to support these claims. These factors were also omitted from their economic analysis. We urge that any conclusions, in the final guidance, regarding potential	Thank you for your comment. The committee makes it conclusions and recommendations after considering all of the relevant evidence including expert advice.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				benefits to the healthcare system be based on objective published evidence.	
156	35	Manufacturer	-	Economic Modelling Model Design Two comparators were selected for the economic analysis: non-rechargeable and rechargeable low frequency SCS, with device longevity being the only assumed difference between rechargeable and non-rechargeable SCS technologies. The de novo analysis should be relevant to the scope as per the MTG Methods Guide. The scope for this submission was the comparison of HF10 therapy using the Senza spinal cord stimulation system versus low frequency spinal cord stimulation. Figure 28 of the sponsor's submission illustrates the decision tree and Markov model that were used to estimate patient flows and costs for a cohort of FBBS patients allocated to SCS + CMM versus CMM alone. The model has been run for three different scenarios, comparing each of the three different types of SCS (Senza HF10 therapy, rechargeable low frequency SCS, non-rechargeable low frequency SCS) to CMM. This is different to the model for TA159 We believe that a model directly comparing the devices included in the scope, rather than an indirect comparison to CMM would have been a more transparent approach. This approach has been utilised in recent MTG 33 on ENDURALIFE powered CRT-D devices for treating heart failure. (7) **SEE APPENDIX 2 FOR REFERENCES**	Thank you for your comment. Please the response to comment number 145. The de novo model submitted by the company was based on that used in TA159, and later updated by Taylor et al. (2010) and Annemans et al. (2014). As all SCS device types are fundamentally similar in terms of indication and outcomes (pain relief), the EAC considered it was appropriate that each was subjected to the same economic analysis and compared with each other (that is, the model structure was the same for all technologies). CMM was not a comparator listed in the scope.
157	18	Manufacturer		This leaves the question as to whether or not a quicker operation which may be possible while peri-operative patient feedback is not required for lead placement may marginally reduce some costs to the NHS to improve the final cost-effectiveness of the system. However, I do not think that this has ever been formally assessed?	Thank you for your comment. Please see the response to comment number 155.
158	19	NHS Professional	4.1	Relying on the evidence from the Senza-RCT study is problematic. Non-Nevro sponsored single arm cohorts have have not shown the same degree of benefit, although benefit, like with other SCS has been	Thank you for your comment. Please see the response to comment 141. The company assigned the same costs to

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				shown. It is this contention of superiority that is problematic. Battery longevity is not all or nothing. At 10 years a Nevro battery having been charged and depleted daily is unlikely to be performing as well as new. The reality is that the patient's recharge burden increases to 2 or 3 times a day. Although one can claim that the battery survival is 10 years. This is one reason why long term outcomes are required. Perhaps re-run the economic model with Nevro batteries lasting 5,6,7,8,9 or 10 years.	either pain state in the model. The consequence of this was that the degree of pain relief, which was the primary outcome of most the clinical studies, had no impact on the company's economic model. The company carried out threshold analysis on battery life. The company reported that if battery life of Senza HF10 was 6.75 years or less, rechargeable SCS would be cost-saving.
159	23	NHS Professional	1.1	Senza-RCT was a FDA non-inferiority study and powered as such so the superiority conclusion of the study is highly questionable. However, I agree it should be included in TA159 guidelines as an equally effective treatment. In real life, tingling sensation is actually a very desirable sensation for many patinets. The improvement in quality of life and functional disability is the outcome of any SCS treatment and not only HF10. Of note, all other modern SCS devices are able to deliver non-tingling stimulation (non-paraesthesia, sub-treshold) including Burst stimulation, Whisper and High-Density. Does the cost mentioned reflect the current list price of the product? I agree use of rechargeable batteries (IPGs) is more cost effective in the long run but this is best decided after assessment of any individual patient's needs, life expectancy, condition being treated and likelihood of continuing with the treatment five years down the line. HF10 technology has only been around for a few years hence extending the current data on device function to 15 years is rather speculative and I would suggest recalculating it on a 8-10 year time frame.	Thank you for your comment. Please see the responses to comments 102 and 134. The EAC consider the superiority of a technology can be concluded even with non-inferiority trial design. Model duration was not a subject of sensitivity analysis. The EAC recalculated the time frame and concluded that if the model duration is reduced to 10 years, the incremental saving associated with Senza HF10 is reduced to: • £2,916 compared with non-rechargeable SCS. • £3,463 compared with rechargeable SCS.
160	24	NHS Professional	-	Appears a well-considered document. Unable to determine the financial aspects of the cost-saving but reassured the document suggests this predictive model has been further investigated and effectively validated.	Thank you for your comment. Please see section 4.27 and table D2 of the assessment report for further details on device longevity model cost parameters.

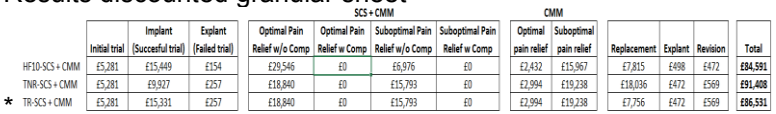
Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Procedure time predictability is related to lack of paraesthesia-mapping often required for low-frequency systems; but is also operator-dependant and subject to other variables, including anatomical differences. Programming is generally observed to be faster due to lack of paraesthesia-mapping in high-frequency mode. In Section 3.9, it is interesting to note that non-rechargeable devices are reported as replaceable every 4 years. Unsure how this was derived, as there is anticipated variability, dependant on programming, usage and other efficiency factors. IPG duration range would be expected alongside average (used in cost model calculations). This was not reported in the document, with inference the data was presented to and confirmed by the committee. The Committee's observations and recommendations for further research / future submissions appear in line with the data available.	
161	29	Manufacturer	1.3	Reliability of section 1.3. The cost summary given in section 1.3 is not reliable. The suggestion that non-rechargeable low-frequency SCS devices need to be replaced every 4 years (as referenced in section 4.14) is not reasonable and is not reflective of real-world experience. For example, Van Buyten et al (2017) showed that the majority of implants had not been replaced at up to 6 years follow up, with approximately 49% being non-rechargeable systems.	Thank you for your comment. Please see the response to comment number 143 and 160.
162	29	Manufacturer	1.3	Reliability of section 1.3. The Institute should check that definitions for the battery lifespan are consistent between Senza and other rechargeable devices, and also the definitions for practical recharging between Senza and other rechargeable devices. If consistent definitions are used, it is likely that there will be no longevity advantage attributable to Senza and this should be reflected in the economic model used to inform section 1.3 of the guidance. For example, Abbotts definition for practical recharging for its Prodigy device is that the device should maintain at least 24 hours of continuous therapy between recharges (It is expected that the Prodigy battery should allow practical recharging for at least ten years). In this definition example, the Senza battery starts life as not having a practical recharging period at all (as a daily recharge is required), and so subsequently a lifespan of zero, therefore immediately battery lifespan definitions need to be unified to draw reasonable comparisons.	Thank you for your comment. Please see the response to comment number 141 and 143.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
163	35	Manufacturer	-	Model inputs Battery Longevity We believe the comparison of HF10 rechargeable to a non-rechargeable system is an unfair comparison due to the limited equivalence in device characteristics and end-user interaction. The Senza device is a rechargeable spinal cord stimulator, thus should be compared to similar paraesthesia-based rechargeable spinal cord stimulators. The Senza RCT only assessed rechargeable devices (Nevro Senza or Boston Scientific Precision Plus); non-rechargeable devices were not included. We recommend that non-rechargeable devices are excluded from the economic modelling and only rechargeable devices are compared. If comparison to a rechargeable must be made, then we request consideration that current data be utilised in the model. Battery technology is evolving rapidly with some non-rechargeable batteries now lasting as long as 9 years therefore the assumption of a 4-year longevity at the time of publication of this guidance is likely to be a significant underestimation of the longevity of newer devices. The technological developments of battery technology, make the use of retrospective data limited in contemporary decision making in the NHS. Medtronic registry data for the Prime-Advance non-rechargeable device demonstrate a mean longevity of 4.84 years. This figure is taken directly from the Kaplan-Meier graph (i.e. no statistical extrapolation). According to the Kaplan-Meier graph, there are 30.9% of devices still active at 6 years and 40% at 65 months. Prime Advanced is a dual channel Implantable Neuromodulation System which is similar to Senza's dual channel (they can both run 2 leads with a total of 16 electrodes). We suggest that these battery longevity data are tested in the economic model as an assumption of a 4.84-year longevity would be likely to reduce the total per patient costs of traditional low frequency SCS in the model. We ask that alternative model time horizons are explored. A 15-year horizon in the original economic model was based on the duration of published data in a study and is favourable to rechargeable devices.	Thank you for your comment. Please see the response to comment number 63, 104, 143 and 159. Non rechargeable low frequency SCS devices are relevant comparators in the scope. The EAC considers the 15 year time horizon to be appropriate.

<table>
<tr><th>Comment no.</th><th>Consultee ID</th><th>Role</th><th>Section</th><th>Consultee comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>We propose running the model with a variety of horizons to fully explore the impact of this upon the results e.g. a 10-year horizon would reflect the warranty provided for the Senza device.

The recent MTG 33 (7) used a time horizon of 6 years based the model’s device survival is based and in line with the scope by being “sufficiently long to reflect any differences in costs and consequences between the technologies being compared”</td><td></td></tr>
<tr><td>164</td><td>35</td><td>Manufacturer</td><td>-</td><td>Economic Modelling
Error in the economic model sub mitted by the sponsor

There is an error in the device descriptions and total costs between the table in the Results Discounted Granular sheet and the Report Tables sheet. In the former table TNR-SCS +CMM has a total cost of £91,408 and £86,531 in the latter. Similarly, TR-SCS +CMM has a total cost of £86,531 in the former and £91,408 in the latter. It is unclear if this has any effect on the model outputs.

Results discounted granular sheet
 
<table>
<tr><th></th><th></th><th colspan="3"></th><th colspan="4">SCS + CMM</th><th colspan="2">CMM</th><th colspan="3"></th><th></th></tr>
<tr><th></th><th></th><th>Initial trial</th><th>Implant (Succesful trial)</th><th>Explant (Failed trial)</th><th>Optimal Pain Relief w/o Comp</th><th>Optimal Pain Relief w Comp</th><th>Suboptimal Pain Relief w/o Comp</th><th>Suboptimal Pain Relief w Comp</th><th>Optimal pain relief</th><th>Suboptimal pain relief</th><th>Replacement</th><th>Explant</th><th>Revision</th><th>Total</th></tr>
<tr><td></td><td>HF10-SCS + CMM</td><td>£5,281</td><td>£15,449</td><td>£154</td><td>£29,546</td><td>£0</td><td>£6,976</td><td>£0</td><td>£2,432</td><td>£15,967</td><td>£7,815</td><td>£498</td><td>£472</td><td>£84,591</td></tr>
<tr><td></td><td>TNR-SCS + CMM</td><td>£5,281</td><td>£9,927</td><td>£257</td><td>£18,840</td><td>£0</td><td>£15,793</td><td>£0</td><td>£2,994</td><td>£19,238</td><td>£18,036</td><td>£472</td><td>£569</td><td>£91,408</td></tr>
<tr><td>*</td><td>TR-SCS + CMM</td><td>£5,281</td><td>£15,331</td><td>£257</td><td>£18,840</td><td>£0</td><td>£15,793</td><td>£0</td><td>£2,994</td><td>£19,238</td><td>£7,756</td><td>£472</td><td>£569</td><td>£86,531</td></tr>
</table>
Report Tables Sheet
<table>
<tr><th></th><th>Total per patient cost</th></tr>
<tr><td></td><td>HF10™ therapy</td><td>£84,591</td></tr>
<tr><td></td><td>Traditional low-frequency SCS (Rechargeable)</td><td>£91,408</td></tr>
<tr><td>*</td><td>Traditional low-frequency SCS (Non-rechargeabl</td><td>£86,531</td></tr>
</table>
)</td><td>Thank you for your comment. The EAC has reviewed the executable model used in the evaluation (without redaction of commercial in confidence data) and can confirm that the discrepancy is limited to a transposition error by Nevro in the naming of cells B78 and B79 in the “ReportTables” tab only.

This naming transposition error has no bearing on the model outputs. Once corrected (by renaming these cells B78 and B79 as ‘Non-rechargeable’ and ‘Rechargeable’ respectively) then the “Total costs” figures for Non-rechargeable (TNR-SCS) and Rechargeable (TR-SCS) low frequency SCS systems transfer correctly from cells C11 and C12 in the “Results_Discounted” tab to the “ReportTables” tab in the executable model. This can be checked and confirmed in the matching sum totals in cells D90 (Non-rechargeable) and D100 (Rechargeable) of the “ReportTables” tab.

The total cost figures quoted in your comment do not match those in the executable model used in the evaluation. The model released to public consultees (on request) had commercial in confidence data removed as requested</td></tr>
</table>

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
					by Nevro. Hence the EAC assumes that the consultee has applied bespoke cost model inputs to generate the total cost figures quoted in this comment.
165	35	Manufacturer	-	Model inputs Long-term SCS efficacy We note that, consistent with the economic model from TA159, there is no movement of patients between the 'Optimal pain relief' and 'Sub-optimal pain relief' states. Patients from these two states instead fail therapy at a rate of 3.24% per year, based on a long-term study by Kumar (2006). (10) This study in fact considered as 'responders' those patients with at least a 50% improvement in pain relief, and a 'failure' was therefore assumed to occur when a patient's pain improvement was less than 50%. This would be consistent with a patient moving from 'optimal' to 'sub-optimal' pain relief. We therefore question whether these data are appropriate for modelling failure of SCS from both health states, and suggest that they should be used to model a gradual movement of patients from optimal to sub-optimal pain relief. **SEE APPENDIX 2 FOR REFERENCES**	Thank you for your comment. The data to inform transition between optimal and suboptimal states of the model is not available, so the model retained the same structural limitation as that used in TA159. In addition, this was a cost-consequence model, therefore movement between these states would have no impact on outputs (please see Section 7.1 of advisory document for further information).
166	35	Manufacturer	-	Model inputs Costing approach As mentioned in the EAC report, costs of drug and non-drug therapy to manage pain are key drivers of the model. Most of the costs, were derived directly from the Taylor et al 2010 (8) economic model used in TA159 technology appraisal. The sponsor inflated these costs using inflation indices. The EAC judged that updating drug costs in this way is not appropriate and considers this a source of uncertainty within the model. We question the validity of inflating these costs to 2016 values, given that some date back as far as 2003, instead of searching for a more realistic estimate of current costs. **SEE APPENDIX 2 FOR REFERENCES**	Thank you for response. Please see section 3.6 and 4.12 of the guidance.
167	30	NHS Professional	-	Are the summaries of clinical and cost consequences reasonable interpretations of the evidence?	Thank you for your comment. The EAC stated that the model assumes equivalent lead placement for Senza HF10 and it

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				Yes, they are. However, it should be clear whether the cost refers to two or four percutaneous leads used (depending on temporary or permanent trial) as well as mention and incorporate the alternative scenario of the cost if a paddle lead (Surpass) is used instead of the percutaneous approach. Is the cost different in that case and how does it compare with a low frequency stimulator system?	comparators, as was reported in The SENZA-RCT. It was not possible to model all possible comparators. Paddle leads were used in 6% of patients in the cohort studied by Van Buyten et al. (2017)
168	5	NHS Professional	-	The MTAC submission mentions cost effectiveness of Senza whilst comparing non-rechargeable traditional devices. Most of the UK implanters use rechargeable traditional devices. The cots effectiveness of Senza device needs to be compared with other rechargeable devices. The charging burden of 30-45 minutes per day needs to be compared with 1-2 hours per week or per mont with other devices.	Thank you for your comment. Please see the response to comment number 163.
169	8	NHS Professional	-	Incorrect costings: Based on expert advice, the committee considered that the low frequency non-rechargeable SCS devices are the most relevant comparator for use in the NHS. We believe based on data from the National Neuromodulation Registry Pilot as well as the advent of Burst Stimulation and other modes of higher charge stimulation, that this statement is erroneous and that the appropriate comparator is rechargeable SCS conventional devices. The cost of other re-chargable devices is similar to Senza.	Thank you for your comment. Please see the response to comment number 104.
170	20	Manufacturer	1.3	Cost Savings We are concerned that this recommendation may be misleading because the £7,755 modelled cost savings in 15 years was associated with traditional non-rechargeable SCS. In the NICE technology appraisal guidance on SCS, NICE recognised that available devices included both rechargeable and non-rechargeable. Since rechargeable SCS should have been considered the comparator in the cost-consequence analysis, the cost saving associated with rechargeable SCS, which are significantly smaller, should be used (£4,795). We are concerned that the guidance states that Senza has a longer lifespan and lower complications rates. Nevros cost model did not include benefits such as 'life-years gained', 'QALY gained.• We would like to highlight a number of issues that diminish the robustness of the model and accuracy of the results. See comment 13 for full comments regarding the cost consequence model.	Thank you for your comment. Please see the response to comment numbers 163 and 165.

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
171	19	NHS Professional	-	7. Conclusions - The economic model presented is flawed. It is out of date (old costs, incomplete assumptions on MRI, wrong comparator) and furthermore the new Senza 2 product will be priced at a premium rate.	Thank you for your response. Please see the response to comment number 77, 145, 163 and 166.
172	29	Manufacturer	1.3	Reliability of section 1.3. It will also be important for the Institute to check whether there are any expected changes in the device and to what extent those changes might impact on cost. Specifically, Senza 2 has just received CE marking. It is reasonable to assume that the will be promotion and adoption of Senza 2. Is this new device expected to be launched in the UK soon and will it be at the same price as the device that is undergoing evaluation? A call between the manufacturer and investors (http://www.nevro.com/English/Investors/Overview/default.aspx) suggested that a new version of Senza 2 would be launched at a premium price to the device that has been assessed. If the price of the new version is higher than that used in the economic model, then the economic model used to inform the draft guidance would be wrong. It would be damaging if the Institute issued guidance that was based on an economic model which rapidly becomes out of date.	Thank you for your response. Please see the response to comment number 145.
173	29	Manufacturer	1.3	Reliability of section 1.3. Differences in trial period length also need to be accounted for in the economic model. HF10 requires a 2-3 weeks trial period compared to 1 week for conventional SCS. The extended trial period for HF10 will in turn place additional burden on NHS services due to the need for more follow up appointments to re-programme the device. These additional attendances need to be factored into the economic model.	Thank you for your comment. Nevro state that the trial period is typically between 5 to 7 days (usually no more than 14 days), depending on the response to the therapy and the doctor's recommendation.
174	35	Manufacturer	-	Model inputs Trial Success The model utilizes the trial success rate solely from the Senza RCT pre-market study. (1) Both the De Andres et al (2) and Thomson et al (3) RCTs fail to replicate the results of Senza RCT and should be considered alongside the claims of clinical superiority and assumptions of short term and long-term efficacy rates expected for real world usage. The model assumes a 92.8% trial success rate, as documented in the single Senza RCT. In the RCT by De Andres et al (2), an 89.6%	Thank you for your comment. Please see the response to comment number 1. De Andres et al. (2017) did not report the proportion of patients who were responders, nor did it provide patient level data with which this could be calculated. Consequently, the EAC concluded that this study could not be used to update the cost-utility study in its current structure. The EAC concluded that Russo et al. (2016), was not comparative and enrolled patients who "were not candidates for, or

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
				(26/29) trial success rate was seen in the HF10 group and 93.5% (29/31) trial success rate for conventional SCS. Using only the Senza RCT pre-market study may artificially inflate the trial-to-implant assumptions for real-world usage. This was data comes from a pre-market study, performed in the USA, thus patients could only receive the "new" treatment by participating in the study. Russo et al (5) evaluated 256 patients and found a 73% trial-to-implant rate for HF-10. This is the largest publication of real-world data on HF-10 and is more likely to reflect clinical practice. We suggest that the data in these studies should be considered in the model assumptions. **SEE APPENDIX 2 FOR REFERENCES**	responders to, traditional SCS therapy", which the EAC infers many patients who did not respond to low frequency SCS did with Senza HF10. Please see the assessment report for further details.

General

Comment no.	Consultee ID	Role	Section	Consultee comments	Response
175	26	Manufacturer	-	Nevro would like to thank the External Assessment Centre for their comprehensive review of the literature and economic model relating to Senza and HF10 Therapy. We are encouraged by the rigour applied to the evaluation and wish to thank both the EAC and the team at NICE for delivering a high quality report which is balanced and evidence-based.	Thank you for your comment.
176	32	Society	-	References: 1. De Andres J, Monsalve-Dolz V, Fabregat-Cid G, Villanueva-Perez V, Harutyunyan A, Asensio-Samper JM, et al. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Med. 2017 Nov 04. PubMed PMID: 29126228. Epub 2017/11/11. 2. Thomson ST, M..Love-Jones, S. Patel,N. Jianwen W,,Que D, Moffitt, M. 29 May - 017. PATIENT RESPONSES TO PARESTHESIA-BASED SPINAL CORD STIMULATION AND KILOHERTZ FREQUENCY	Thank you for your comment.

				SPINAL CORD STIMULATION: at International Neuromodulation Societys 13th World Congress Neuromodulation: Technology Changing Lives Edinburgh, Scotland, United Kingdom May 27“June 1, 2017. Abstract at Neuromodulation. 2017;20:e336“e783.	
177	18	Manufacturer		The principal, professional, society which ought to have been approached for comment on this appraisal is the Neuromodulation Society of the UK and Ireland (NSUKI). This society represents the greatest number of clinicians who actually deliver SCS, I would have thought that the committee would have included this group in their scope.	Thank you for your comment. The Neuromodulation Society of the UK and Ireland (NSUKI) is a registered stakeholder for this evaluation.
178	26	Manufacturer	-	Suggest change to "functional ability’ instead of functional disability’ to align with improvement descriptor.	Thank you for your comment. This has been amended.
179	29	Manufacturer	2.4	Claim: Sustained and long-term improvement in pain relief and function, which may reduce the need for pain medication and follow-up attendance at pain clinics. The use of may raises concerns over the ability to judge this claim. Have reductions in pain medication and follow up attendance at pain clinics been proven within the published evidence? If not, this claim cannot be supported. It is our understanding that use of HF10 increases the number of follow up visits relative to conventional spinal cord stimulation because patients have to make more visits to clinic to assess whether the device is delivering pain control.	Thank you for your comment. Section 2.4 reflects the company's claimed benefits. The committee makes the recommendations presented in section 1 after considering all of the relevant evidence including expert advice.
180	32	Society	-	The British Pain Society recommends the biopsychosocial model of pain and any treatment recommendations for the management of chronic pain should involve the multi-disciplinary team in assessing and advising pain management strategies including self-management of pain to ensure successful rehabilitation. It is often seen that the implantation of a neurostimulator alone would not relieve pain and could result in explanting the device. It is recommended that neuromodulation is considered as part of a multimodal strategy in pain management.	Thank you for your comment. The committee considered this comment and received clinical expert advice which agreed with your comment and informed the committee it was reflective of their own practice. The committee decided to amend section 1.2 of the guidance to reflect this.

Appendix 1

Please find below the references included in comments 7, 8, 37, 65, 66, 84, 85, 91, 109, 110 and 148 above:

- Annemans, L., Van Buyten, J. P., Smith, T., & Al-Kaisy, A. (2014). Cost effectiveness of a novel 10 kHz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS). J Long Term Eff Med Implants, 24(2-3), 173-183. Retrieved from http://www.dl.begellhouse.com/journals/1bef42082d7a0fdf,0134a0a71af442c9,63d1c2fa20ed74ea.html

- Berg, A. P., Mekel-Bobrov, N., Goldberg, E., Huynh, D., & Jain, R. (2017). Utilization of multiple spinal cord stimulation (SCS) waveforms in chronic pain patients. Expert Rev Med Devices, 14(8), 663-668. doi:10.1080/17434440.2017.1345621

- Bicket, M. C., Dunn, R. Y., & Ahmed, S. U. (2016). High-Frequency Spinal Cord Stimulation for Chronic Pain: Pre-Clinical Overview and Systematic Review of Controlled Trials. Pain Med, 17(12), 2326-2336. doi:10.1093/pm/pnw156

- De Andres, J., Monsalve-Dolz, V., Fabregat-Cid, G., Villanueva-Perez, V., Harutyunyan, A., Asensio-Samper, J. M., & Sanchis-Lopez, N. (2017). Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Med. doi:10.1093/pm/pnx241

- de Vos, C. C., Bom, M. J., Vanneste, S., Lenders, M. W., & de Ridder, D. (2014). Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation, 17(2), 152-159. doi:10.1111/ner.12116

- Deer, T. R., Mekhail, N., Provenzano, D., Pope, J., Krames, E., Leong, M., . . . North, R. (2014). The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation, 17(6), 515-550; discussion 550. doi:10.1111/ner.12208

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