Washington State Health Care Authority

Spinal cord stimulation

Assessing signals for update

July 31, 2018

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Spinal Cord Stimulation: Assessing Signals for Update

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July 31, 2018

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Previous coverage decision

A Health Technology Assessment titled: Spinal Cord Stimulation, was originally released on July 23, 2010 by the Washington State Health Technology Clinical Committee. Additionally, two update signal assessments were published on December 29, 2014 and August 29, 2016. The Committee's Coverage Decision for the original report is summarized below, followed by the main conclusions from the 2014 and 2016 Signal Update reviews.

Health Technology Background

The Spinal Cord Stimulation topic was selected and published in December 2009 to undergo an evidence review process. Spinal Cord Stimulation (SCS) is an alternative treatment proposed for patients with chronic neuropathic pain who have not responded to conventional therapies such as medication, physical and/or psychological therapy, and in some case, re-operation. Current best evidence is available primarily from four trials on 375 patients; which are rated at a Level 1 or 2 (good quality), which is a better level of evidence than some interventions. However, total patient sample size is small, comparators were weak or inappropriate, reported outcomes are mostly subjective and not consistently reported, industry funding and management may have an impact, and no trial included a sham stimulation/procedure arm. The overall body of evidence was inconsistent, with several trials showing benefits on some outcomes at generally shorter follow up periods and others showing no difference. SCS is an implanted, long term treatment, but no evidence exists on either long term efficacy or safety.

The committee agreed that SCS is less safe than alternatives, is an invasive procedure, and has many adverse events. While conventional medical management is not invasive, so would generally have a lower risk profile, re-operation is also a comparator and had less complications. SCS device related complications can be serious and include dural punctures, amplitude by bodily movements; paresthesia in other body parts, pain, disturbed urination, lead fracture, loss of effect, infection. Indications for SCS (FDA): Chronic intractable pain in the trunk and/or limbs including unilateral or bilateral pain associated with FBSS and intractable low back and leg pain, and for some devices: CRPS, radicular pain syndrome or radiculopathies resulting in pain, post-laminectomy pain, unsuccessful disc surgery, degenerative disc disease or herniated disc pain refractory to conservative or surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, and multiple back surgeries. Potential patients should undergo a period of trial stimulation prior to permanent SCS implantation. Contraindications for SCS (FDA): Failed trial stimulation due to ineffective pain relief; poor surgical risks; pregnancy; active general infections or multiple illnesses; inability to operate the SCS system; and cardiac pacemakers (with specific exceptions and precautions) or cardioverter defibrillators.

In June 2010, the HTA posted a draft and then followed with a final report from a contracted research organization that reviewed publicly submitted information; searched, summarized, and evaluated trials, articles, and other evidence about the topic. The comprehensive, public and peer reviewed Spinal Cord Stimulation report is 164 pages, and identified a relatively large amount of literature.

An independent group of eleven clinicians who practice medicine locally meet in public to decide whether state agencies should pay for the health technology based on whether the evidence report and other

presented information shows it is safe, effective and has value. The committee met on August 20, reviewed the report, including peer and public feedback, and heard public and agency comments. Meeting minutes detailing the discussion are available through the HTA program or online at http://www.hta.hca.wa.gov under the committee section.

Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

(1) Evidence availability and technology features

The committee concludes that the best available evidence on Spinal Cord Stimulation has been collected and summarized.

- Spinal Cord Stimulation (SCS) is an alternative treatment proposed for patients with chronic neuropathic pain who have not responded to conventional therapies such as medication, physical and/or psychological therapy, and in some case, re-operation.
- Current best evidence is available primarily from four trials on 375 patients; which are rated at a Level 1 or 2 (good quality), which is a better level of evidence than some interventions. However, total patient sample size is small, comparators were weak or inappropriate, reported outcomes are mostly subjective and not consistently reported, industry funding and management may have an impact, and no trial included a sham stimulation/procedure arm. The overall body of evidence was inconsistent, with several trials showing benefits on some outcomes at generally shorter follow up periods and others showing no difference.
- SCS is an implanted, long term treatment, but no evidence exists on either long term efficacy or safety.

(2) Is it safe?

The committee concludes that the comprehensive evidence indicates that Spinal Cord Stimulation is less safe than alternative treatments. Key factors to the committee's conclusion included:

- The committee agreed that SCS is less safe than alternatives, is an invasive procedure, and has many adverse events. While conventional medical management is not invasive, so would generally have a lower risk profile, re-operation is also a comparator and had less complications. SCS device related complications can be serious and include dural punctures, amplitude by bodily movements; paresthesia in other body parts, pain, disturbed urination, lead fracture, loss of effect, infection.
- The committee agreed that safety was a significant factor: the number of trial reported complications ranged from 8 to 100%. Device related complication requiring revision ranged from 25% to 38% of patients in short term and 42% to 60% in up to 5 years (not including 54% of patients undergoing pulse generator replacements due to battery life).

- The committee agreed that there were currently no reported mortality rates, but that the FDA data was not available and the small sample size is likely underpowered to detect.
- The committee agreed that the removal rate could be considered an efficacy or safety issue, but the rates ranging from 4% to 17% were concerning, especially considering that trial stimulation is done first on all patients.

(3) Is it effective?

The majority of the committee concludes that the comprehensive evidence about Spinal Cord Stimulation effectiveness is unproven.

- The committee agreed that the studies had serious limitations in design, low patient sample sizes, and weak or inadequate comparators. Additionally, placebo effects of a new intervention for patients with chronic pain who have already failed multiple therapies is a serious concern and no study involved sham stimulation or procedures and outcome measures were generally subjective.
- The committee found that evidence overall on important patient outcomes was limited. For all outcomes, there is no evidence of longer term improvement, particularly important when there are significant risks (including 1/3 revision and high removal rate) and the device is intended for permanent implant.
- Given the serious limitations of the studies, the committee agreed that, at best, weak evidence exists that SCS may provide temporary improvement of pain in some patients, but there is no evidence of mid or long term pain improvement.
- While pain is a critical patient outcome, evidence about other important patient outcomes was either not available or not consistent with the pain findings.
    - For instance, for reduction in pain medication in short term: Kumar and Turner found no difference, while North found SCS patients did have reduction.
    - For functional improvements, 1 trial found short term functional improvement, but 2 others did not; and there was no reliable evidence of functional improvement at mid (or long) term.
- For all other outcomes, including improvement in quality of life, there is no reliable evidence of effect.

(4) Evidence about the technology's special populations, patient characteristics and adjunct treatment

The committee agreed that no compelling evidence exists to differentiate sub groups or special populations.

- The committee agreed with the evidence based report that there is inadequate evidence to identify characteristics that either enhance or reduce the efficacy of SCS such as age, sex, workers' compensation or other disability payments, duration of pain, pain intensity, time since first lumbar surgery, number of prior operations for pain, pain location, laterality of pain, allodynia or hypoesthesia at baseline, McGill Pain Questionnaire or the Minnesota Multiphasic Personality Inventory (MMPI)

(5) Is the technology cost-effective?

- The committee concludes that SCS is unproven to be cost effective.
- The committee agreed that the cost of SCS is substantial, averaging $27,000 per patient.
- The committee agreed that overall value cannot be ascertained without evidence of net benefit of effectiveness and reduced harm. Reliable cost-effectiveness analysis cannot be performed.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee concluded that the current evidence on Spinal Cord Stimulation demonstrates that there isn't sufficient evidence to cover the use of Spinal Cord Stimulation for chronic neuropathic pain. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted 8 to 1 to not cover Spinal Cord Stimulation.

The committee reviewed the Clinical guidelines and Medicare decision. The Medicare decision was did not cite evidence and was decided prior to any of the studies reviewed by the committee. The guidelines recommendations conflict and not all have reviewed the latest trials included in this report.

Conclusions of the 2014 Signals for Update Assessment - SCS

***Key Question* 1**: What is the evidence of efficacy and effectiveness of spinal cord stimulation?

Efficacy: All conclusions are still valid and this portion of the CER does not need updating.
Effectiveness: All conclusions are still valid and this portion of the CER does not need updating.

Key Question 2: What is the evidence of the safety of spinal cord stimulation?

All conclusions are still valid and this portion of the CER does not need updating.

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?

All conclusions are still valid and this portion of the CER does not need updating.

Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

This section of the report could be updated with the results of the cost-effectiveness analysis of the cohort of Washington State workers' compensation patients with FBSS (Hollingworth 2011)3.

However, the addition of this analysis (which suggests that SCS is not cost-effective in this patient population compared with pain clinic or usual care) would not affect the coverage decision (SCS is not covered).

Conclusions of the 2016 Signals for Update Assessment – SCS

Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?

With respect to efficacy, two studies compared SCS to conventional treatment in patients with diabetic neuropathy. Both found a short term pain improvement in favor SCS. There were no assessments of function or quality of life. Both studies report complications, some serious, to include serious infection and dural puncture leading to death. Three studies looked at new applications of SCS, high frequency SCS and burst stimulation. All were short term (1 or 2 weeks) crossover studies in patients who were already receiving traditional SCS. While burst stimulation shows some promise in these early cross-over studies, longer follow-up studies that compare burst stimulation in parallel arms to both non-stimulation therapy and placebo are needed in patients naïve to stimulation. Unfortunately, there are no current studies registered in ClinTrials.gov making these assessments, Appendix C. The five new RCTs evaluated in this signal report do not invalidate the previous evidence (criteria A-1 or A3), nor provide major changes in the evidence (criteria B-1 – B4).

Key Question 2**:** What is the evidence of the safety of spinal cord stimulation?

With respect to safety of spinal cord stimulation, data from two studies continue to underscore that SCS is not without complications and do not invalidate the previous evidence (criteria A-2)

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?

There is no new evidence with respect to differential efficacy or safety of SCS in subpopulations.

Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

A new cost-utility study does not invalidate the previous evidence (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).

1. Purpose of Report

A prior update report was completed in October 2010 and signal update assessments in January 2014 and August 2016. The purpose of this additional literature update is to determine whether or not there is sufficient evidence published after the previous signal assessments to conduct a further review of this technology. The key questions from the original report are listed below:

Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?

Key Question 1: What is the evidence of the safety of spinal cord stimulation?

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?

Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

2. Methods

2.1 Literature Searches

We conducted a limited literature search for articles published between May 1, 2016 and June 29, 2018 that addressed key questions 1 through 4. This search included three main databases: PubMed/Medline and Cochrane Library. We used key words to detect articles that used the terms “spinal cord stimulation”, “spinal cord stimulator”, or “spinal cord stimulation”. Appendix A includes the search methodology for this topic. Additionally, we reviewed ClinicalTrials.gov for relevant ongoing studies (Appendix B).

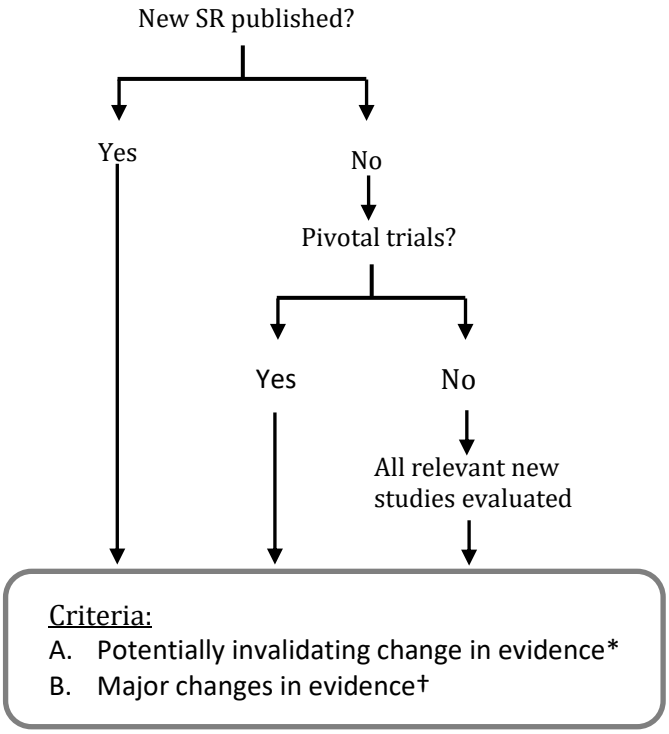
2.2 Study Selection

We sought systematic reviews (SR) of randomized controlled trials (RCTs) of efficacy and safety with meta-analysis that included articles that met inclusion and exclusion criteria similar to the original report and previous signal updates. In addition we sought SRs reflecting updates or new advances for the technology. Consistent with the previous report and updates, case-series specifically designed to evaluate safety with at least 5 years of follow-up were considered.

2.3 Compilation of Findings and Conclusions

For this assessment we abstracted the data from the included studies and constructed a demographics/results table (see Appendix C). We also constructed a summary table that included the key questions, the original conclusions, conclusions from prior updates, new sources of evidence, new findings, and conclusions based on available signals, Table 1 below. To assess whether the conclusions are still relevant, we used an algorithm based on a modification of the Ottawa method, Figure 1.

Figure 1. Algorithm of the modified Ottawa Method of Identifying Signals for SR Update3. Results



*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment

B-3. Clinically important caveat

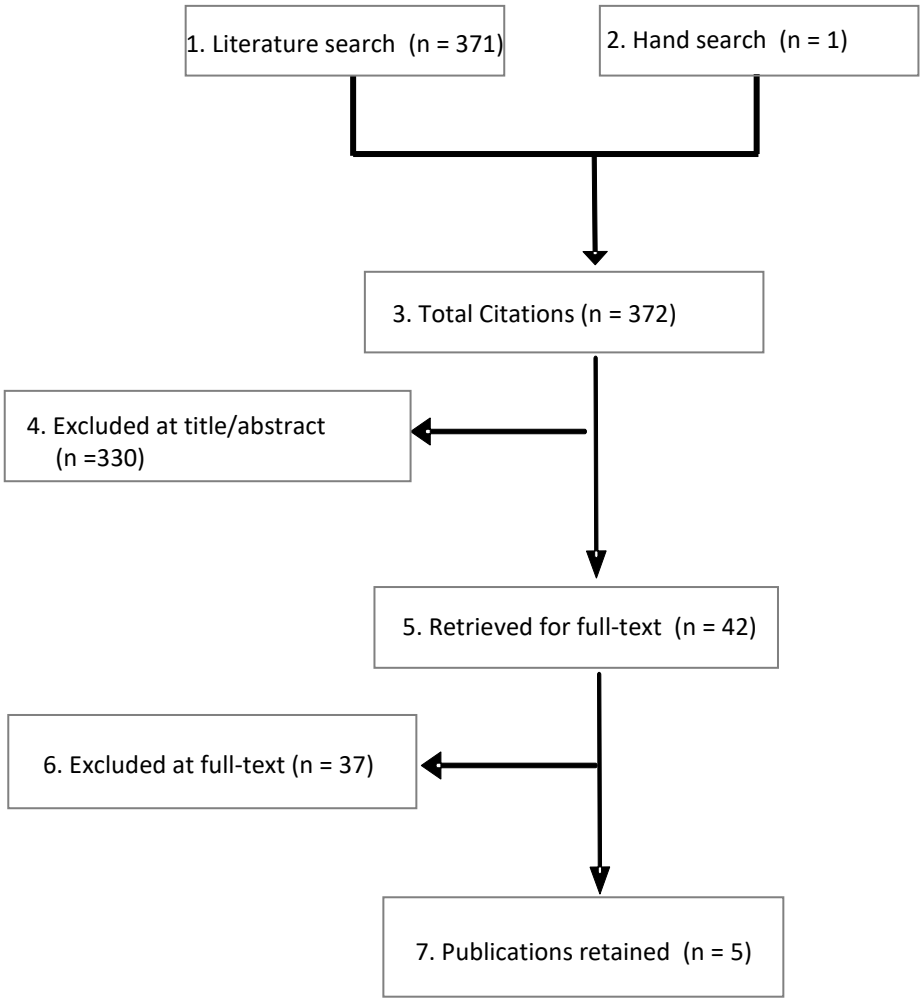
B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

3.1 Search

From 372 citations identified (via literature search plus hand searching), 330 were excluded at title/abstract review. Of the remaining 42 reviewed at full-text, five studies that addressed key questions 1–4 in part or in full were retained (Figure 2), including three RCTs, one case series specifically evaluating safety, and one cost-utility analysis. No new systematic reviews with quantitative synthesis of relevant RCTs were identified in keeping with the focus on new evidence of efficacy. Comparative observational

studies evaluating effectiveness were not sought. Consistent with the prior report and updates, studies that compared different frequencies or modes of spinal cord stimulation with each other only were excluded. Additionally, studies of dorsal root ganglion stimulation were excluded as this technology is different from spinal cord stimulation due to its action on peripheral nerves. Dorsal root ganglion stimulation was FDA approved via the PMA process in 2016. A full list of excluded studies and the reasons for exclusions can be found in Appendix D.

Figure 2. Flow chart showing results of literature search



3.2 Identifying Signals for Re-review

Table 1 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the recommendations of Aggregate Analytics, Inc. (AAI) regarding the need for update. Appendix B includes updated information on currently ongoing trials assessing spinal cord stimulators.

Table 1. Summary Table of Key Questions 1-6

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?				
1. a) Efficacy (Short-term, <5 years): • **Pain, perceived effect of treatment/patient satisfaction:** There is moderate evidence from three small randomized controlled trials that SCS is superior to conventional therapies (conservative medical management [CMM], physical therapy or re-operation) in patients with chronic neuropathic pain during the first 2–3 years with respect to patient reported outcomes of pain, and perceived effect of treatment/patient satisfaction. In the only RCT that measured outcomes for a longer period of time, the benefit of SCS decreased over time and was not significantly different than controls for leg pain after 3 years of treatment (see mid-term below). • **Function, quality of life:** The effect on quality of life outcomes is less clear with one RCT reporting substantial benefit of SCS compared with CMM at 6 months follow-up, while another study found	2014: This section of the report is still valid and does not need updating (no new data identified). 2016: 5 new RCTs (de Vos 2014, Slangen 2014, Schu 2013, De Ridder 2013, Perruchoud 2013) do not invalidate the previous evidence (criteria A-1 or A3), nor provide major changes in the evidence (criteria B-1 – B4).	3 RCTs Al-Kaisy (2018)[1] Durate (2016)[2] Kriek (2017)[4]	All RCTs reported **short-term efficacy**. There were no data available to assess mid-term or long-term efficacy. **SCS vs. Conventional Medical Practice (CMP)** One small parallel-design RCT (Durate) compared CMP supplemented with SCS versus CMP alone in patients with diabetic neuropathy. Follow-up was 6 months. • **Pain and quality of life (QoL):** SCS resulted in a statistically significant improvement in pain intensity and health-related QoL compared with CMP alone. The mean difference between groups in VAS (0-10) pain of 3.7 may be clinically meaningful. **SCS vs. sham** Two small cross-over trials (with various levels of industry involvement) compared different frequencies of SCS with each other and with sham (Al-Kaisy, Kriek); one trial also included burst SCS (Kriek). Both trials had very short follow-up of 2 or 3 weeks. • **Pain:** Across RCTs, results were conflicting which may be due to	This section of the report is still valid and does not need updating (criteria A-1 or A-3; B-1–4).

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
quality of life outcomes to be similar between SCS + physical therapy and physical therapy alone at 2 years follow-up. Similarly, function as measured by the Oswestry Disability Index score was better in the SCS group at 6 months versus CMM in one study but the ability to perform daily activities after 3 years was not different in a second study. The strength of this evidence is low. **b) Efficacy (Mid-term, 5-10 years):** • **Pain, quality of life, perceived effect of treatment:** There is low evidence from one small randomized controlled trial that SCS is no different from conventional therapy (physical therapy) in patients with chronic neuropathic pain 5-10 years following implant with respect to pain, quality of life, and patient-reported global perceived effect. **c) Efficacy (Long-term, ≥10 years):** • There are no data available to assess long-term efficacy. **2. a) Effectiveness (Short-term, <5 years):** • **Composite of pain, function, and opioid use:** One prospective cohort study on workers' compensation patients reported similar success on a composite score that includes pain, function and opioid use between SCS and either Pain Clinic or			differences in methodology and pathology. Compared with sham, one trial in patients with FBSS found that SCS performed at a frequency of 5882 Hz, but not at 3030 or 1200 Hz, resulted in statistically significant back pain relief; in the second trial SCS at all tested frequencies (40, 500, and 1200 Hz) and burst SCS were significantly better in patients with CRPS. Mean differences between groups were not reported; informal estimates suggest differences of 1.6 to 2.5 on VAS (0-10), which may not be clinically meaningful. • **Global perceived effect (GPE):** For self-assessed "improvement" on the GPE scale in one trial, SCS at 40 and 500 Hz were significantly better than sham, but no difference was seen between sham and 1200 Hz or burst SCS. For GPE satisfaction, all active SCS settings including burst were significantly better than sham stimulation.	

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
Usual Care treatment groups. There was a modest improvement in leg pain in the SCS group compared with the control groups at 6 months follow-up but this did not persist at the 12 month or 24 month evaluation. **b) Effectiveness (Mid- and long-term, ≥5 years):** There are no data available to assess mid- or long-term effectiveness.				
Key Question 2: What is the evidence of the safety of spinal cord stimulation?				
1. Revision • There is high evidence from three randomized controlled trials, one prospective comparative cohort study and six case series that revision of SCS components is not uncommon. Overall short-term revision rates ranged from 12–38% of patients. Mid-term revision rates were 42% in one RCT and 60% in one case series. Reasons for revision include electrode repositioning or replacement, generator revision or replacement, revision of the connecting cable, and total removal and replacement of the system due to infection. There are no long-term data available. **2. Other SCS-related side effects**	2014: This section of the report is still valid and does not need updating (3 case series: Falowski 2011, Kumar 2011, Wolter 2012) 2016: Two new studies (de Vos 2014, Slangen 2014) do not invalidate the previous evidence (criteria A-2)	2 RCTs Al-Kaisy (2018)[1] Kriek (2017)[4] 1 case series Nissen (2018)[5]	Two small cross-over trials (with various levels of industry involvement) compared different frequencies/settings of SCS with each other and with sham; one trial also included burst SCS (Kriek). Both trials had very short follow-up of 2 or 3 weeks. Comparative data was limited. Additionally, one case series was identified that reported mid-term (median 5 year) complication rates. **Revision.** *Short-term* revision rates were 4% (due to pain at IPG site) and 10% (due to electrode dislocation) of patients across the two trials. In the latter trial, an additional eight instances of electrode reconfiguration was reported (unclear if the 8 refers to patients or events). The other trial also notes that 12.5% of patients had radiographically confirmed "minor" lead migration but do not mention whether or not these patients required revision. *Mid-term* revision rates were 37% overall in the case series; the revision rate due specifically to	This section of the report is still valid and does not need updating (criteria A-2).

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
• Side effects reported varied widely among studies and included infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, severe wound-related pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma. The rate of side effects could not be determined from the papers reviewed; however, one RCT reported that all patients experienced at least one side effect. **3. Mortality** • There is high evidence that the rate of mortality due to SCS is low. Among the four comparative studies, 2 deaths were reported in patients receiving SCS (2/139); one as a result of a cardiac event six months following SCS implantation, and the cause of one was not reported. No deaths were recorded in the control groups during the same time period (0/179). Two additional deaths were identified in three case series with five year follow-up; one from a cerebrovascular accident in a patient implanted for cardiac ischemic pain, one as a result of suicide. No death was attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.			complications was 14% (included deep infection, hardware malfunction, hematoma, IPG discomfort, and electrode migration). **Other SCS-related side effects** varied across the trials and only one trial provided comparative data for some outcomes (Kriek 2017). Over the *short-term*, itching and/or rash was more common with SCS vs. sham (6.9% vs. 0%); the same number of patients in both groups experienced headache (3.4%). Other adverse events (not reported by group) included axial paresthesia (3.4%) in one trial, and skin heating during recharging (4.2%) and intercostal pain (4.2%) in the other. No serious adverse events were reported to include infection or neurological sequelae. At *mid-term* follow-up in one case series, the overall infection rate was 3.1% and there were no neurological injuries requiring surgical intervention. **Mortality** was not reported by either trial or the case series.	

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?				
1. Age • There is conflicting evidence whether patient age at baseline is associated with outcome. Two studies found that age did not correlate with either pain relief or success (combination of pain relief and patient satisfaction), while one study found that younger age was correlated with pain relief of at least 50%. One of these studies also reported no correlation between age and SF-36 or GPE scores. **2. Sex** • There are mixed results regarding whether patient sex is associated with outcome following SCS. Three studies found that sex was not associated with pain relief, one showed no correlation between sex and SF-36 or GPE scores. In contrast, one study found that females had a significantly higher rate of success (pain relief and patient satisfaction), improved function and activity, and decreased medication usage at five years compared with males. **3. Workers' compensation or other disability payments** • One prospective study suggests that whether patients receive workers' compensation/other disability payments or no compensation has no effect on pain	2014: This section of the report is still valid and does not need updating (no new data identified). 2016: No new data.	No new evidence	No new evidence	No new data.

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
relief among patients receiving SCS. Another prospective study found that among patients on workers' compensation, successful outcomes of pain relief, improved function and reduced opioid use was similar between SCS and two control treatment groups. The percentages of success were low in all groups. **4. Duration of pain** • There is moderate evidence from three cohort studies that duration of pain prior to SCS implantation is not associated with pain relief or success within the first year after implantation. **5. Pain intensity** • There is low evidence from one cohort study to suggest that pain intensity at baseline is not associated with success. **6. Time since first lumbar surgery** • There is low evidence from one cohort study to suggest that time since first lumbar surgery is not predictive of success.				
Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulation?				
Cost Effectiveness • There is moderate evidence from three complete economic evaluations that in the short-term, SCS is associated with improved outcomes and increased costs	2014: This section of the report could be updated with the results of the cost-effectiveness analysis of the cohort of Washington State	Slagen 2017[6]	Slagen et al conducted a cost-utility analysis alongside a multicenter RCT comparing SCS versus best medical treatment in patients with painful diabetic peripheral neuropathy. The time horizon was 12 months in the base case analysis. From societal and payer perspectives,	This section of the report is still valid and does not need updating (criteria A-1 or A3; B-1).

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
compared with CMM and/or re-operation for the treatment of neuropathic pain. In the long-term, SCS appears to be dominant over the control treatments; however, only one study included in this assessment was conducted in a U.S. setting. More specifically, we found that there is some evidence that SCS is cost-effective at moderate (<$20,000) incremental cost effectiveness ratio (ICER) levels compared with CMM or re-operation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or re-operation) assuming device longevity of 4 years and at least a 30% pain threshold criteria. However, the assumption of continued efficacy past 3 years is questionable from the only RCT reporting pain 5-10 years after implantation. Furthermore, only one study was conducted in a US setting.	workers' compensation patients with FBSS. However, the addition of this analysis (which suggests that SCS is not cost-effective in this patient population compared with pain clinic or usual care) would not affect the coverage decision (SCS is not covered) (Hollingworth 2011, Kemler 2010). 2016: One new cost-utility (Zucco 2015) study does not invalidate the previous evidence (criteria A-1 or A3), nor provide major changes in the evidence (criteria B-1).		ICERs were €94,159.56/QALY and €34,518.85/QALY, respectively. From the societal perspective, at a willingness-to-pay threshold of €80,000, SCS would be cost-effective in only 46% of cases. The authors conclude that SCS is not cost-effective in the short-term in this patient population, primarily due to the high initial investment costs of SCS. Sensitivity analyses testing the impact of baseline differences in costs and extending the depreciation period of the SCS material to 4 years, indicated that SCS is likely to become cost effective over the longer-term.	

AAI = Aggregate Analytics, Inc.; CRPS = complex regional pain syndrome; FBSS = failed back surgery syndrome; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; RCTs = randomized controlled trials; SCS = spinal cord stimulation.

4. Conclusions

Table 1 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the conclusions of AAI with respect to the criteria that identify a trigger for an update (Figure 1).

4.1 Key Question 1: With respect to efficacy, one new small RCT compared SCS versus conventional medical practice in patients with diabetic neuropathy and reported short-term (6 months) improvements in pain and quality of life in favor of SCS. Two new small crossover trials with very short follow-up (2 or 3 weeks) compared different frequencies of SCS versus sham; one trial also included burst SCS. Results were inconsistent. In the trial evaluating patients with failed back surgery syndrome (FBSS), SCS performed at a frequency of 5882 Hz, but not at 3030 or 1200 Hz, resulted in statistically significant pain relief compared with sham. The second trial included patients with complex regional pain syndrome and found that SCS performed at all tested frequencies (40, 500, and 1200 Hz) and burst SCS provided statistically better pain relief. It is difficult to draw conclusions across these two trials given the variability in methodology and pathology. Across all three trials, although authors report statistically significant improvement in pain it is unclear whether these differences are clinically meaningful. There were no data available to assess mid-term or long-term efficacy. The three new RCTs do not provide major changes in the evidence. This section of the report is still valid and does not need updating (criteria A-1 or A3; B-1–4).

4.2 Key Question 2: With respect to safety of SCS, short-term data from two new small crossover trials (comparing burst SCS and SCS at various frequencies with sham stimulation) and mid-term data from one new case-series in patients with FBSS show similar frequencies of complications as those previously reported and continue to underscore that SCS is not without complications. This section of the report is still valid and does not need updating (criteria A-2).

4.3 Key Question 3*:* There is no new evidence with respect to differential efficacy or safety of SCS in subpopulations.

4.4 Key Question 4*:* With respect to cost-effectiveness, one new cost-utility analysis of SCS versus best medical treatment in patients with diabetic peripheral neuropathy concluded that SCS is not cost-effective in the short-term, primarily due to the high initial investment costs of SCS. This section of the report is still valid and does not need updating (criteria A-1 or A3; B-1).

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1. Al-Kaisy A, Palmisani S, Pang D, et al. Prospective, Randomized, Sham-Control, Double Blind, Crossover Trial of Subthreshold Spinal Cord Stimulation at Various Kilohertz Frequencies in Subjects Suffering From Failed Back Surgery Syndrome (SCS Frequency Study). Neuromodulation : journal of the International Neuromodulation Society 2018.

2. Duarte RV, Andronis L, Lenders MW, de Vos CC. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2016;25:1771-7.

3. Hollingworth W, Turner JA, Welton NJ, Comstock BA, Deyo RA. Costs and cost-effectiveness of spinal cord stimulation (SCS) for failed back surgery syndrome: an observational study in a workers' compensation population. Spine 2011;36:2076-83.

4. Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJ. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial. European journal of pain (London, England) 2017;21:507-19.

5. Nissen M, Ikaheimo TM, Huttunen J, Leinonen V, von Und Zu Fraunberg M. Long-Term Outcome of Spinal Cord Stimulation in Failed Back Surgery Syndrome: 20 Years of Experience With 224 Consecutive Patients. Neurosurgery 2018.

6. Slangen R, Faber CG, Schaper NC, et al. A Trial-Based Economic Evaluation Comparing Spinal Cord Stimulation With Best Medical Treatment in Painful Diabetic Peripheral Neuropathy. The journal of pain : official journal of the American Pain Society 2017;18:405-14.

APPENDIX A. SEARCH STRATEGIES

The detailed strategy below is presented in Medline and EMBASE syntax.

Search Strategy
(May 1, 2016 and June 29, 2018)
Limited to English language, human population

Database: PUBMED/MEDLINE

1.	"Spinal cord stimulation" OR "Spinal cord stimulation"[MeSH] OR "spinal cord stimulator" OR "spinal cord stimulators"
2.	#1 NOT "Case Reports"[Publication Type]

Database: EMBASE

'spinal cord stimulation'/exp OR 'spinal cord stimulator'/exp AND [humans]/lim AND [English]/lim AND [abstracts]/lim AND [5-1-2013]/sd NOT [12-1-2013]/sd AND [2010-2014]/py

Parallel strategies were used to search the Cochrane Library and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches
The following databases have been searched for relevant information:
Cochrane Database of Systematic Reviews (through 2009, Issue 2)
PubMed (1975 through July 23, 2009)

Additional Economics, Clinical Guideline and Gray Literature Databases
Food and Drug Administration (FDA)
Google
ClinicalTrials.gov

APPENDIX B. CURRENT COMPARATIVE STUDIES IN ClinTrial.gov ASSESSING SCS (accessed July 25, 2018)

NCT Number	Tittle	Conditions	Interventions	Control	Enrollment	Funder	Start Date	Completion Date
NCT03595241	PANACEA Feasibility Study to Assess the Efficacy of BurstDR Spinal Cord Stimulation (SCS) (PANACEA)	• Abdominal Refractory Visceral Pain	• Burst DR SCS	• No intervention	30	• Other	July 30, 2018	December 1, 2019
NCT03586882	Effect of Spinal Cord Stimulation on Gait and Balance in Chronic Low Back Pain Patients	• Chronic Low Back Pain	• SCS	• No Intervention	100	• Other Industry	June 15, 2018	February 2020
NCT03546738	Spinal Cord Burst Stimulation for Chronic Radicular Pain Following Lumbar Spine Surgery	• Back Pain With Radiation • Pain, Postoperative	• Burst SCS	• Sham	50	• Other	June 15, 2018	February 8, 2023
NCT03470766	Sham-Controlled RCT on 10kHz High-Frequency Spinal Cord Stimulation for Chronic Neuropathic Low Back Pain (Modulate-LBP) (Modulate-LBP)	• Chronic Low Back Pain • Neuropathic Pain • Refractory Pain	• Nevro Senza • System (HF10 SCS Therapy)	• Sham	96	• Other	August 1, 2018	August 1, 2020
NCT03462147	Efficacy of Spinal Cord Stimulation in Patients With a Failed Back Surgery Syndrome. (HDS)	• Back Pain	• High Density SCS • Conventional SCS	• Sham	10	• Other	October 1, 2017	December 31, 2018
NCT03419312	PET Patterns, Biomarkers and Outcome in Burst SCS Treated FBSS Patients	• FBSS • Pain, Intractable • Low Back Pain • Radicular; Neuropathic, • Lumbar, Lumbosacral	• Burst SCS	• Sham	12	• Other	February 11, 2018	June 2019

NCT Number	Tittle	Conditions	Interventions	Control	Enrollment	Funder	Start Date	Completion Date
NCT03228420	Comparison of 10 kHz SCS Combined With CMM to CMM Alone in the Treatment of Neuropathic Limb Pain	• Painful Diabetic • Neuropathy	• Senza HF10 • SCS Therapy	• CMM	360	• Other	July 20, 2017	December 31, 2018
NCT01550575	Precision Retrospective Outcomes (PRO)	• Chronic Pain	• Non Boston • Scientific SCS • Boston Scientific • Precision Plus SCS	• CMM	10000	• Industry	March 2012	December 2022
NCT01162993	Effect of Spinal Cord Stimulation (SCS) in Painful Diabetic Polyneuropathy	• Diabetic Neuropathies	• SCS	• No Intervention	40	• Other	April 2010	January 2018

APPENDIX C. SUMMARY OF INCLUDED STUDIES

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
Al-Kaisy (2018)[1] Cross-over RCT	N = 30 Male: 16/24 (66.7%) Age: 47.9 (range, 33 - 60) F/U: 12-weeks (3-weeks per frequency) % F/U: 80% (24/30) Diagnosis: FBSS Intervention vs. control • 1200 Hz @ 180 µsec vs. • 3030 Hz @ 60 µsec vs. • 5882 Hz @ 30 µsec vs. • Sham	VAS back pain score (Mean ± SD)* • Sham: 4.83 ± 2.45 • 1200 Hz: 4.51 ± 1.87 • 3030 Hz: 4.57 ± 2.09 • 5882 Hz: 3.22 ± 1.98 Pairwise comparison of VAS back pain scores • 5882 Hz vs. sham: mean difference = 1.61, adjusted p-value = 0.003 • 1200 Hz vs. sham: NS • 3030 Hz vs. sham: NS Mean % reduction in VAS back pain scores • Sham: 34.9% • 1200 Hz: 40.6% • 3030 Hz: 39.8% • 5882 Hz: 57.1% Mean average leg pain scores • Sham: 2.51 • 1200 Hz: 2.37 • 3030 Hz: 2.20 • 5882 Hz: 1.81 (NS difference between groups, p=0.367) Patient Preference (reported either very satisfied or somewhat satisfied w/ therapy) • Sham: NR • 1200 Hz: 63% • 3030 Hz: 63% • 5882 Hz: 75% (p NR) Patients' Global Impression of Change	This randomized crossover study demonstrated that 5882 Hz stimulation can produce significant pain relief for axial low back pain compared with lower frequencies and sham stimulation. Sham stimulation produced similar analgesic effects to 1200 Hz and 3030 Hz and this effect may influence future neuromodulation clinical trial designs.	• Differences in charge per second may have partially influenced the outcome • Blinding cannot be guaranteed • Prior to randomization, 3 subjects were withdrawn by the study investigators for no specified reason • No wash out period between cross-overs • Short follow-up of 3-weeks • Potential for recall bias Adnan Al-Kaisy received travel sponsorship and speaker fees from Medtronic and Nevro Corp, he is the principal investigator in separate studies sponsored by Medtronic, Nevro Corp and Abbot and he has financial interest in Micron Device LLC. Stefano Palmisani received speaker fees and sponsorships to attend professional meetings from Nevro Corp and Medtronic; David Pang received sponsorship to attend professional meetings from Medtronic and Nevro Corp. Ye Tan and Sheryl McCammon are employees of Medtronic.

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		• Sham: - No change: 9/24 (37.5%) - Somewhat better: 10/24 (41.7%) - Better: 5/24 (20.8%) • 1200 Hz: - No change: 6/24 (25%) - Somewhat better: 14/24 (58.3%) - Better: 4/24 (16.7%) • 3030 Hz: - No change: 4/24 (16.7%) - Somewhat better: 14/24 (58.3%) - Better: 4/24 (16.7%) • 5882 Hz: - No change: 2/24 (8.3%) - Somewhat better: 12/24 (50%) - Better: 10/24 (41.7%) (Freidman's test, p-value = 0.007) <u>Patients chosen stimulation frequency at the end of the 12-week cross-over period</u> • Sham: 12.5% • 1200 Hz: 21% • 3030 Hz: 12.5% • 5882 Hz: 29% Reverted to traditional simulation: 25% **Safety:** <u>Pain at implanted pulse generator site</u> 3/24 (12.5%) (1 subject required lead replacement)		

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		Minor lead migration (radiologically confirmed) 3/24 (12.5%) Skin heating during recharging 1/24 (4.2%) Intercostal pain 1/24 (4.2%) Infection 0/24 (0%) Adverse neurological sequelae 0/24 (0%)		
Duarte (2016)[2] RCT	N = 60 Male: 38/60 (63%) Age: 59 (SD, 11) F/U: 6-months % F/U: 90% (54/60) Diagnosis: Refractory diabetic neuropathic pain in the lower extremities Intervention vs. control • CMP + SCS vs. • CMP alone	Reduction in pain intensity, %Δ from baseline (SCS vs. CMP) • CMP + SCS - Minimally clinically important (10-30%): 4/36 (11%) - Moderately important (30-50%): 3/36 (8%) - Substantial clinical difference (≥50%): 24/36 (67%) - NR: 5/36 (14%) • CMP alone - Minimally clinically important (10-30%): 6/18 (33%) - Moderately important (30-50%): NR - Substantial clinical difference (≥50%): 1/18 (6%) - NR: 11/18 (61%) VAS for Pain Intensity (Mean (SD)) • CMP + SCS: 29 (27) • CMP alone: 66 (22) - (SCS vs. CMP mean difference = -37, 95% CI -52 to -22, p < 0.001) EQ-5D index (Mean (SD))†	SCS resulted in significant improvement in pain intensity and QoL in patients with PDN, offering further support for SCS as an effective treatment for patients suffering from PDN. From a methodological point of view, different results would have been obtained if QALY calculations were not adjusted for baseline EQ-5D scores, highlighting the need to account for imbalances in baseline QoL.	• Did not employ ITT (6 patients not included in 6-month follow-up analysis • Statistically significant differences in baseline QALY score for which investigators had to adjust for retrospectively. • Open label design • Lack of placebo None

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		• CMP + SCS: 0.65 (0.28) • CMP alone: 0.44 (0.33) (SCS vs. CMP mean difference = 0.21, 95% CI 0.04 to 0.39, p < 0.05) EQ-VAS (Mean (SD)) • CMP + SCS: 61 (23) • CMP alone: 41 (20) (SCS vs. CMP alone mean difference = 20, 95% CI -7 to -34, p < 0.01) QALYS – unadjusted for baseline EQ-5D score • CMP + SCS: 0.226 • CMP alone: 0.220 (Difference = 0.006, 95% CI 0.070 to 0.085, p = NS) QALYS – adjusted for baseline EQ-5D score • CMP + SCS: 0.258 • CMP alone: 0.178 (Difference = 0.080, 95% CI 0.044 to 0.114, p < 0.001) Between group differences in EQ-5D dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression) • NS for all dimensions except Pain/Discomfort (p < 0.001) Proportion of CMP alone patients choosing to cross-over to the CMP + SCS group after 6-months 14/18 (78%) Proportion of CMP + SCS patients choosing to continue CMP + SCS therapy after 6-months 34/36 (94%)		
Kriek (2017)[4] ISRCTN 36655259 Cross-over RCT	N = 33 Male: 4/29 (14%) Age: 42.55 (SD, 12.83)	VAS (mean (SE) [95% CI]) • Standard 40 Hz SCS: 39.83 (4.7) [30.19–49.47]; p<0.05 vs. sham	The results from this trial allow to conclude that stimulation with 40, 500, 1200 Hz and burst	• Did not employ ITT (4 patients not included in follow-up analysis) • Short wash out period of 2 days

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
	F/U: 10-weeks (2-weeks per frequency) % F/U: 88% (29/33) Diagnosis: CRPS Intervention vs. control • Standard 40 Hz SCS vs. • 500 Hz SCS vs. • 1200 Hz SCS vs. • Burst SCS vs. • Placebo (sham)	• 500 Hz SCS: 40.13 (4.94) [30.02–50.24]; p<0.05 vs. sham • 1200 Hz SCS: 42.89 (4.79) [33.09–52.70] ; p<0.05 vs. sham • Burst SCS: 47.98 (5.26) [37.22–58.75] ; p<0.05 vs. sham • Placebo (sham): 63.74 (3.51) [56.56–70.91] P<0.05 for all SCS groups vs. sham McGill average pain score (mean (SE) [95% CI])‡ • Standard 40 Hz SCS: 4.70 (0.40) [3.89–5.50] • 500 Hz SCS: 5.10 (0.45) [4.18–6.03] • 1200 Hz SCS: 5.31 (0.46) [4.36–6.26] • Burst SCS: 5.66 (0.49) [4.65–6.66] • Placebo (sham): 7.07 (0.28) [6.50–7.63] p<0.05 for all SCS groups vs. sham GPE for Satisfaction (mean (SE) [95% CI])§ • Standard 40 Hz SCS: 5.28 (0.29) [4.69–5.86] • 500 Hz SCS: 5.31 (0.27) [4.76–5.86] • 1200 Hz SCS: 4.97 (0.26) [4.43–5.50] • Burst SCS: 4.72 (0.34) [4.02–5.43] • Placebo (sham): 3.52 (0.35) [2.79–4.24] p<0.05 for all SCS groups vs. sham GPE for Improvement (mean (SE) [95% CI])§ • Standard 40 Hz SCS: 4.93 (0.20) [4.53–5.34]; p<0.05 vs. sham • 500 Hz SCS: 5.00 (0.23) [4.53–5.47]; p<0.05 vs. sham • 1200 Hz SCS: 4.72 (0.21) [4.29–5.15]; p=NS vs. sham • Burst SCS: 4.55 (0.24) [4.06–5.05]; p=NS vs. sham • Placebo (sham): 3.79 (0.27) [3.24–4.34]	are equally effective in relieving neuropathic pain related to CRPS and are significantly better than placebo. Some patients prefer standard stimulation over the newer, non-standard stimulation settings. However, even though higher frequencies and burst SCS are promising, we should not discard standard stimulation as a therapeutic option. More importantly, standard SCS therapy has proven to be safe and effective when used for prolonged periods of time. The best solution for the future is to incorporate all the various stimulation modalities into one device so that the patient can receive the stimulation which provides the best pain relief and user-friendliness and to make it possible for them to switch between various frequency settings if needed, either during the trial-SCS period of	• All patients were pre-treated with standard SCS prior to entering crossover period; may not be generalizable to patients naïve to stimulation • Blinding cannot be ensured considering placebo and burst SCS did not elicit paresthesia, and the differences in charging time per each frequency • Potential for recall This investigator-initiated study was supported by a grant from St. Jude Medical (Plano, TX, USA). The design, performance, analysis and submission of this trial were independently performed by our research group. FH is a paid consultant for Grunenthal GmbH; DdR has a patent on burst stimulation and is a paid consultant for St. Jude Medical.

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		Preferred Stimulation • Standard 40 Hz SCS: 14/29 (48.3%) • 500 Hz SCS: 6/29 (20.7%) • 1200 Hz SCS: 4/29 (13.8%) • Burst SCS: 4/29 (13.8%) • Placebo (sham): 1 (3.4%) p=NR Best user-friendliness • Standard 40 Hz SCS: 14/29 (48.3%) • 500 Hz SCS: 8/29 (27.6%) • 1200 Hz SCS: 1/29 (3.4%) • Burst SCS: 6/29 (20.7%) • Placebo (sham): 0/29 (0%) p=NR Most Comfortable • Standard 40 Hz SCS: 14/29 (48.3%) • 500 Hz SCS: 7/29 (24.1%) • 1200 Hz SCS: 4/29 (13.8%) • Burst SCS: 4/29 (13.8%) • Placebo (sham): 0/29 (0%) p=NR **Safety:** Serious adverse events 0/29 (0%) Electrode dislocation 3/29 (10.3%) (n=1, lead revised and continued trial; n=2 lead revised but did not continue trial) Electrode reconfiguration required 8 events Itching and/or rash 2/29 (6.9%)	during regular SCS therapy. Ultimately, the field of neuromodulation should move towards customized individual patient care.	

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		Axial paresthesia 1/29 (3.4%) Headache 4 events		
Nissen (2018)[5] Case series (retrospective)	N = 175 (224 patients enrolled, 49 did not experience adequate pain relief during trial period and did not receive a permanent SCS) Male: 52% Age: median 48 (22-83) years F/U: 6 (0-18) years Diagnosis: FBSS Intervention: SCS	**Safety:** • Device explantation: 26% (45/175) ○ Inefficient pain relief: 76% (34/45) ○ IPG depletion: 6% (3/45) ○ No further need for SCS: 6% (3/45) ○ Surgical site infection**:** 2% (1/45) (permanent explanation) ○ Electrode migration: 2% (1/45) ○ IPG region discomfort: 2% (1/45) ○ Need for MRI: 2% (1/45) ○ Unsuccessful implantation: 2% (1/45) • Revision: 37% (64/175) (70 total revisions)** • Revision due to complications: 14% (25/175) (26 total revisions) ○ Deep infection: 24% (6/25) (7 total: 6 revisions, 1 removal) ○ Hardware malfunction (extension lead, electrode or IPG replacement; SCS removal and re-implantation): 40% (10/25) (11 total revisions) ○ Subcutaneous hematoma: 4% (1/25) ○ Discomfort over pulse generator: 12% (3/25) (4 total: 3 revisions, 1 removal) ○ Electrode migration: 8% (2/25) (3 total: 2 revisions, 1 removal) • Revision due to inadequate pain relief: 11% (19/175) (22 total revisions) ○ Electrode repositioning: 15 revisions ○ Electrode replaced: 2 revisions ○ Explantation and new trial: 3 revisions	**Safety Summary:** • Two out of 3 patients with permanent SCS after the trial did not need additional surgery during the follow-up period. • The complication rate was 14%, which is markedly less than the 30% to 40% reported previously. Complications were mainly minor and did not lead to serious neurological sequelae. • The infection rate (3%) was in line with previous studies, reporting 3% to 6% infection rates. All infections appeared less <1 month after an operation, indicating that long-term subclinical infections are rare. Only 1 patient had a permanent	• During the study, neurosurgeons performing implantations changed • Criteria for permanent SCS implantation changed over the course of the study • Most patients in the study received an electrode that is not used presently. Funding was from a Government Research Fund. Dr Nissen has received travel funding from the Medtronic, Boston Scientific and Abbott St Jude Medical. Ms Ikäheimo, Dr Huttunen, and Dr von und zu Fraunberg have received travel funding from the Medtronic and Abbott St Jude Medical. Dr Leinonen has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		○ Explantation and immediate new SCS: 2 revisions • Revision due to IPG battery depletion: 11% (20/175) (22 total revisions) • Infection (overall): 3.1% Neurological injuries requiring surgical intervention: 0%	explantation due to an infection.	
Slangen (2017)[6] Cost-utility Study	N = 36 Male: 24/36 (66.7%) Age (mean ± SD): SCS, 57.1 ± 12.4 years; BMT, 56.5 ± 8.0 years F/U: 3, 6, and 12 months % F/U: 3-months, 32/36 (88.9%); 6-months, 33/36 (91.7%); 12-months, 17/22 (77.3%)†† Diagnosis: Diabetic Peripheral Neuropathy Intervention vs. control • SCS + BMT (n=22) vs. • BMT (n=14) Cost-utility analysis • Perspective: Societal and Payer • Time Horizon: 12-months • Performed alongside multi-center RCT • QALY calculated using utility scores from the EuroQol 5	**Economic**: **Societal Perspective** ICER (SCS + BMT relative to BMT) • €94,159.56 Total Costs at 12-months • SCS + BMT: €26,539.18 vs. • BMT: €5,313.45 Effectiveness at 12-months (QALY) • SCS + BMT: .58 vs. • BMT: .36 Probability Cost Effective with a WTP Threshold = €80,000 • 46% **Healthcare Perspective** ICER (SCS + BMT relative to BMT) • €34,518.85 Total Costs at 12-months • SCS + BMT: €18,742.18 vs. • BMT: €2,173.13 Effectiveness at 12-months (% Successfully treated pts.) • SCS + BMT: 55% vs. • BMT: 7% Probability Cost Effective with a WTP Threshold = €80,000	SCS was not cost effective compared with BMT at the 12-month follow-up, mainly because of the high initial investment costs of SCS. Secondary analyses showed that the ICER decreased considerably when correcting for baseline differences in costs, and extending the depreciation period of the SCS material to 4 years.	• In 3 patients, only baseline data was present (although ITT was employed) • Part of the cost data were collected retrospectively (potential for recall bias) • Data of the BMT group were linearly extrapolated up to 12 months, assuming no change between 6- and 12- months in this group • Short-term cost-utility only, no long-term data None

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
	• Primary outcome: ≥50% pain relief or a score of ≥6 on GPE scale at 12 months§ • Cost discounted at 4%/year • Cost in 2012€ • Nonparametric bootstrap analysis and sensitivity performed	• NR		

Abbreviations: BMT, Best Medical Treatment; CMP, Conventional Medical Practice; CRPS, Complex Regional Pain Syndrome; EQ-5D, Euro Qualified 5 Dimensions; FBSS, Failed Back Surgery Syndrome; GPE, Global Perceived Effect; ICER, Incremental Cost Effectiveness Ratio; IPG, Implantable Pulse Generator; ITT, Intention to Treat; NR, Not Reported; NS, Not significant; QALY; Quality Adjusted Life Years; SCS, Spinal Cord Stimulation; VAS, Visual Analog Scale; WTP, Willingness to Pay.

* The average pain scores for back pain from the last three days of complete diary data during the last week of each blinded crossover assignment was the primary efficacy outcome.

† EQ-5D utility scores at baseline were ALSO statistically significantly different between SCS and CMP groups.

‡ The McGill Pain Questionnaire recorded the Numerical Rating Scale (NRS) of average pain, minimum pain, maximum pain and pain during exertion (scale 0–10: 0 = no pain and 10 = worst pain ever).

§ The GPE score reporting satisfaction and the improvement on a 7-point Likert scale. Lower GPE scores are indicative for more severe conditions (satisfaction scale: 7 = very satisfied to 1 = not at all satisfied; improvement scale: 7 = completely recovered to 1 = worse than ever).

** Study is unclear in defining how removals differ from revisions. Data has been abstracted as it was presented in the article.

†† Patients in the BMT group (n=14) were not evaluated at 12-month follow-up because after 6 months they were offered SCS.

APPENDIX D. LIST OF EXCLUDED ARTICLES AFTER FULL-TEXT REVIEW

Study	Reason for Exclusion:
Systematic Reviews	
Aiyer R, Barkin RL, Bhatia A, Gungor S. A systematic review on the treatment of phantom limb pain with spinal cord stimulation. Pain management 2016;7:59-69.	No new RCTs since previous report
Amirdelfan K, Webster L, Poree L, Sukul V, McRoberts P. Treatment Options for Failed Back Surgery Syndrome Patients With Refractory Chronic Pain: An Evidence Based Approach. Spine 2017;42 Suppl 14:S41-s52.	No new RCTs since previous report
Bicket MC, Dunn RY, Ahmed SU. High-Frequency Spinal Cord Stimulation for Chronic Pain: Pre-Clinical Overview and Systematic Review of Controlled Trials. Pain medicine (Malden, Mass) 2016;17:2326-36.	Comparison of different SCS modalities, no non-SCS controls
Cho JH, Lee JH, Song KS, et al. Treatment Outcomes for Patients with Failed Back Surgery. Pain physician 2017;20:E29-e43.	No new RCTs since previous report
Cruccu G, Garcia-Larrea L, Hansson P, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. European journal of neurology 2016;23:1489-99.	No new RCTs since previous report
Deer TR, Campos LW, Pope JE. Evaluation of Abbott's BurstDR stimulation device for the treatment of chronic pain. Expert review of medical devices 2017;14:417-22.	Comparison of different SCS modalities, no non-SCS controls
Dy SM, Bennett WL, Sharma R, et al. AHRQ Comparative Effectiveness Reviews. Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017.	No new RCTs since previous report
Grider J. Effectiveness of spinal cord stimulation in chronic spinal pain: a systematic review. Pain physician 2016;19:E33-E54.	No new RCTs since previous report
Hou S, Kemp K, Grabois M. A Systematic Evaluation of Burst Spinal Cord Stimulation for Chronic Back and Limb Pain. Neuromodulation : journal of the International Neuromodulation Society 2016;19:398-405.	Comparison of different SCS modalities, no non-SCS controls
Kapural L, Peterson E, Provenzano DA, Staats P. Clinical Evidence for Spinal Cord Stimulation for Failed Back Surgery Syndrome (FBSS): Systematic Review. Spine 2017;42 Suppl 14:S61-s6.	No new RCTs since previous report
Tajti J, Szok D, Majlath Z, Csati A, Petrovics-Balog A, Vecsei L. Alleviation of pain in painful diabetic neuropathy. Expert opinion on drug metabolism & toxicology 2016;12:753-64.	No new RCTs since previous report
Visnjevac O, Costandi S, Patel BA, et al. A Comprehensive Outcome-Specific Review of the Use of Spinal Cord Stimulation for Complex Regional Pain Syndrome. Pain practice : the official journal of World Institute of Pain 2017;17:533-45.	No new RCTs since previous report

Study	Reason for Exclusion:
Waszak PM, Modric M, Paturej A, et al. Spinal Cord Stimulation in Failed Back Surgery Syndrome: Review of Clinical Use, Quality of Life and Cost-Effectiveness. Asian spine journal 2016;10:1195-204.	No new RCTs since previous report
Zyluk A, Puchalski P. Effectiveness of complex regional pain syndrome treatment: A systematic review. Neurologia i neurochirurgia polska 2018.	No new RCTs since previous report
RCTs	
Amirdelfan K, Yu C, Doust MW, et al. Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2018.	Comparison of different SCS modalities, no non-SCS controls
De Andres J, Monsalve-Dolz V, Fabregat-Cid G, 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 medicine (Malden, Mass) 2017;18:2401-21.	Comparison of different SCS modalities, no non-SCS controls
Deer T, Slavin KV, Amirdelfan K, et al. 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 2018;21:56-66.	Comparison of different SCS modalities, no non-SCS controls
Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain 2017;158:669-81.	Comparison of SCS to DRG stimulation
Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. Neurosurgery 2016;79:667-77.	Comparison of different SCS modalities, no non-SCS controls
Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MW. Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation. Neuromodulation : journal of the International Neuromodulation Society 2016;19:492-7.	Comparison of different SCS modalities, no non-SCS controls
Safety	
Bendel MA, O'Brien T, Hoelzer BC, et al. Spinal Cord Stimulator Related Infections: Findings From a Multicenter Retrospective Analysis of 2737 Implants. Neuromodulation : journal of the International Neuromodulation Society 2017;20:553-7.	Case Series with inadequate follow-up (<5 years)
van Buyten JP, Wille F, Smet I, et al. Therapy-Related Explants After Spinal Cord Stimulation: Results of an International Retrospective Chart Review Study. Neuromodulation : journal of the International Neuromodulation Society 2017;20:642-9.	Case Series with inadequate follow-up (<5 years)

Study	Reason for Exclusion:
Chan AK, Winkler EA, Jacques L. Rate of perioperative neurological complications after surgery for cervical spinal cord stimulation. Journal of neurosurgery Spine 2016;25:31-8.	Case Series with inadequate follow-up (<5 years)
Dupre DA, Tomycz N, Whiting D, Oh M. Spinal Cord Stimulator Explantation: Motives for Removal of Surgically Placed Paddle Systems. Pain practice : the official journal of World Institute of Pain 2018;18:500-4.	Case Series with inadequate follow-up (<5 years)
Fitzgibbon DR, Stephens LS, Posner KL, et al. Injury and Liability Associated with Implantable Devices for Chronic Pain. Anesthesiology 2016;124:1384-93.	Case Series with inadequate follow-up (<5 years); also looking at liability claims, relevant outcomes not reported
Hoelzer BC, Bendel MA, Deer TR, et al. Spinal Cord Stimulator Implant Infection Rates and Risk Factors: A Multicenter Retrospective Study. Neuromodulation : journal of the International Neuromodulation Society 2017;20:558-62.	Duplicate study (see Bendel et al 2017 above); case Series with inadequate follow-up (<5 years)
Khan H, Kumar V, Ghulam-Jelani Z, et al. Safety of Spinal Cord Stimulation in Patients Who Routinely Use Anticoagulants. Pain medicine (Malden, Mass) 2017.	Case Series with inadequate follow-up (<5 years)
Kleiber JC, Marlier B, Bannwarth M, Theret E, Peruzzi P, Litre F. Is spinal cord stimulation safe? A review of 13 years of implantations and complications. Revue neurologique 2016;172:689-95.	Case Series with unclear follow-up
Maldonado-Naranjo AL, Frizon LA, Sabharwal NC, et al. Rate of Complications Following Spinal Cord Stimulation Paddle Electrode Removal. Neuromodulation : journal of the International Neuromodulation Society 2017.	Case Series with inadequate follow-up (<5 years)
Moeschler SM, Warner NS, Lamer TJ, et al. Bleeding Complications in Patients Undergoing Percutaneous Spinal Cord Stimulator Trials and Implantations. Pain medicine (Malden, Mass) 2016;17:2076-81.	Case Series with inadequate follow-up (<5 years)
Moufarrij NA. Epidural hematomas after the implantation of thoracic paddle spinal cord stimulators. Journal of neurosurgery 2016;125:982-5.	Case Series with unclear follow-up; highlights several case reports
Pope JE, Deer TR, Falowski S, et al. Multicenter Retrospective Study of Neurostimulation With Exit of Therapy by Explant. Neuromodulation : journal of the International Neuromodulation Society 2017;20:543-52.	Case Series with unclear follow-up; relevant outcomes NR
Sanchis-Lopez N, Romero-Garcia C, De Andres-Ibanez J, et al. Medical Device Related Pressure Injury in the Treatment of Chronic Pain: An Early Sign of Explantation in Suspected Infection. Pain physician 2018;21:E235-e46.	Mixed SCS (63%) and intrathecal drug delivery (ITDD) pumps (37%), outcomes not reported separately; case series with unclear f/u
Yusuf E, Bamps S, Thuer B, et al. A Multidisciplinary Infection Control Bundle to Reduce the Number of Spinal Cord Stimulator Infections. Neuromodulation : journal of the International Neuromodulation Society 2017;20:563-6.	Case series with inadequate f/u; focus is to evaluate an intervention to reduce SCS infections

Study	Reason for Exclusion:
Economic Studies	
Farber SH, Han JL, Elsamadicy AA, et al. Long-term Cost Utility of Spinal Cord Stimulation in Patients with Failed Back Surgery Syndrome. Pain physician 2017;20:E797-e805.	Not a full economic study
Han JL, Murphy KR, Hussaini SMQ, et al. Explantation Rates and Healthcare Resource Utilization in Spinal Cord Stimulation. Neuromodulation : journal of the International Neuromodulation Society 2017;20:331-9.	Not a full economic study
Hoelscher C, Riley J, Wu C, Sharan A. Cost-Effectiveness Data Regarding Spinal Cord Stimulation for Low Back Pain. Spine 2017;42 Suppl 14:S72-s9.	Search date included time period of previous report