Spinal Cord Stimulation Assessing Signals for Update

Provided by:

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Aug 29, 2016

Contents

Previous Coverage Decision

A Comparative Effectiveness Review (CER) titled: SPINAL CORD STIMULATION, was originally released in July 2010 by the Health Technology Clinical Committee and summarized below.

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.

1. Purpose of Report

A prior update report was completed in January 2014. The purpose of this literature update is to determine whether there is sufficient evidence published after the last update to conduct a re-review of this technology.

2. Methods

2.1 Literature Searches

We conducted a limited literature search for articles published between Aug 1, 2013 and Aug 21, 2016 using the identical search strategy used for the original report. This search included four main databases: PubMed, Medline, Cochrane Library, and EMBASE. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general, we used the same inclusion and exclusion criteria as the original CER.

2.3 Compilation of Findings and Conclusions

For this assessment we abstracted the data from the included studies and constructed a demographics table, Table 1. We also constructed a summary table that included the key questions, the original conclusions, the prior update data, new sources of evidence, new findings, and conclusions based on available signals, Table 2. To assess whether the conclusions might need updating, we used an algorithm based on a modification of the Ottawa method, Figure 1.

3. Results

3.1 Search

A systematic review was undertaken for articles published between Aug 1, 2013 and Aug 21, 2016. We used search strategies to identify articles from MEDLINE, EMBASE and the 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. Among the articles describing the efficacy and/or safety of spinal cord stimulation, we evaluated the full text to determine if the studies met our inclusion criteria. Full text of potential articles meeting the inclusion criteria by both methods were reviewed to obtain the final collection of included studies, Figure 2.

The literature search identified 411 titles. After title and abstract review, we further reviewed the full text of 19 journal articles. The remaining 392 titles were rejected because they were case reports, commentary, or did not include topics of interest. Among the 19 articles that went on to full text review, 13 were rejected because subjects did not meet the inclusion criteria and/or did not include a comparison of interest, Appendix B. No new systematic reviews with quantitative synthesis of relevant literature were identified.

3.2 New SCS applications

Since our report, we identified two new strategies for electrical waveform delivery for SCS; high frequency SCS (HFSCS) (at 10,000 Hz) and burst SCS. Traditional SCS has a pulse width of 400 μsec and a stimulation rate of 40 Hz.[1] The objective of traditional (tonic) SCS is to induce a paresthesia that overlaps with the painful region.

High-frequency stimulation delivers the energy at a higher frequency (most studies use 10,000 Hz), while burst stimulation delivers 40 Hz bursts of 5 spikes at 500 Hz. Both methods of stimulation provide modulation of the nervous system without the patient perceiving paresthesia. This is done by reducing the amplitude to subthreshold levels.

3.3 Studies identified (Table 1)

No systematic reviews were identified that contained new RCTs with a quantitative analysis of results (meta-analysis). Therefore, we identified relevant trials and summarize them below.

Two small trials compared SCS with a control group. de Vos et al[2] randomized 60 patients to receive SCS (n = 40) or conventional pain treatment (n=20) in those with painful diabetic neuropathy. The mean age was 59.5 years and 63% were male. The follow-up period was 6 months. The investigators reported that 60% of the SCS group and 5% of the control group achieved >50% pain reduction at follow-up (p<.001). The mean reduction in VAS pain (0-100 scale) over baseline was 42 for the SCS group and 0 for the control (p<.001). Adverse events included pain due to the implanted pulse generator (n=2) and electrode lead migration (n=1); perceived incomplete overlap of the paresthesia with the painful area during trial stimulation requiring placement of a second electrode lead (n=2); infection during trial stimulation (n=1) that was successfully resolved and followed by a permanent implantation; and coagulopathy, which complicated the implantation procedure and prolonged hospitalization (n=1). Limitations of this study include an open label design, a lack of a placebo control, no functional or quality of life outcomes, and vagueness of allocation concealment.

Slangen et al[3] randomized 36 patients to receive SCS plus best medical treatment (n = 22) or best medical treatment alone (n=14) in those with painful diabetic neuropathy. The mean age was 56.9 years and 67% were male. The follow-up period was 6 months. The investigators reported that 41% of the SCS group and 0% of the control group achieved >50% pain reduction during the day, and 36% vs. 7% at night at follow-up (p<.001). Patient's Global Impression of Change for pain and for sleep were also better in the SCS group compared with control: 55% and 36% vs. 0% and 0%, respectively, p<.01). There were two serious adverse events in this trial. One patient sustained a dural puncture during implantation of a lead for test stimulation, followed by subdural hematoma and death; and one patient had an infection of the SCS system 6 weeks after implantation with a slow but incomplete recovery. Limitations of this study include an open label design, a lack of a placebo control, no functional or quality of life outcomes,and vagueness of allocation concealment.

Three small industry sponsored cross-over RCTs compared either HFSCS or burst SCS to placebo stimulation. Schu et al[4] treated 20 patients with failed back surgery syndrome (FBSS) and a preexisting SCS system. Each received three treatment allocations in random order for a period of one week: tonic SCS (500-Hz), burst SCS, and placebo stimulation. The mean age was 58.6 years, and 35% were male. The investigators reported that burst SCS reduced pain intensity as measured by the numerical rating scale (NRS) after one week compared with placebo: 4.7 ±2.5 vs. 8.3 ±1.1, p<.05. Pain quality as measured by the short form McGill Pain Questionnaire (SFMPQ) was also better in the burst vs. placebo group: 19.5 ±10.5 vs. 33.5 ±11.8, p<.05. Eighty percent of the patients preferred burst SCS over placebo, tonic or conventional SCS, p= .0004. Limitations of this study include a very short follow-up of only 1 week, no wash out period between cross-over periods, and a study population with stable benefit from conventional SCS (i.e., results may not be generalizable to patients naïve to stimulation).

Likewise, de Ridder et al[5] treated 15 patients that had a preexisting SCS system, 12 who had FBSS. Each received three treatment allocations in random order for a period of one week: traditional tonic SCS, burst SCS, and placebo stimulation. The mean age was 54.1 years, and 27% were male. The investigators reported that burst SCS reduced axial, limb and general pain as measured by the percent change over baseline in VAS (0-100 mm) after one week compared with placebo: 51.3%, 52.7%, 55.0%

vs. 18.9%, 11.7% and 10.9%, respectively, p<.05 for each outcome. Attention to pain and changes in pain as measured by the Pain Vigilance and Awareness Questionnaire (PVAQ) were also better in the burst vs. placebo group: 7.6% and 10.0% vs. 3.3 and 3.2%, respectively, p<.05 for each outcome. Limitations of this study include a very short follow-up of only 1 week, no wash out period between cross-over periods, and a study population with stable benefit from conventional SCS (i.e., results may not be generalizable to patients naïve to stimulation). Furthermore, the principle author holds a patent for burst stimulation.

Perruchoud et al[6] treated 33 of 38 study participants that had chronic low back pain and used a preexisting SCS system. Each received their current (conventional) SCS followed by either HFSCS (10,000 Hz) or placebo stimulation selected randomly, followed by conventional SCS followed by either HFSCS or placebo, whichever treatment was not given earlier. The period lasted one week. The mean age was 54.2 years, and 48% were male. The primary outcome measure was the Patient's Global Impression of Change (PGIC). The investigators reported no difference between HFSCS and placebo with respect to the proportion of PGIC reporting at least "minimal improvement", (42.4% vs. 30.3%), p = .30. There were no differences between treatment groups in VAS pain nor EQ-5D. The authors note a significant "period effect"; patients who had a either HFSCS or placebo first did better than those who had HFSCS or placebo second. Limitations of this study include a very short follow-up of only 2 weeks, no wash out period between cross-over periods, and a study population with stable benefit from conventional SCS (i.e., results may not be generalizable to patients naïve to stimulation).

One cost effectiveness and cost utility study of SCS in patients with FBSS was reported.[7] The authors used a before-after design where patients with predominant leg pain refractory to conventional medical treatment (CMM) expecting to receive SCS were recruited in 9 Italian centers and followed up to 24 months after SCS. They collected data on clinical status, Health-Related Quality-of-Life (HRQoL) and on direct and indirect costs retrospectively before and prospectively after the SCS intervention. Costs were quantified in € 2009, adopting the National Health Service's (NHS) and societal perspectives. They included 80 patients. The mean age was 58 years, and 40% were male. The utility gained during the 12-24 month post-SCS period corresponds to a QALY increase of 0.173, generating a cost per QALY gained of €47,000 and of €38,372 from the NHS and societal points of view, respectively. The authors conclude that the cost-utility acceptability curve suggests that, if decision makers' willingness to pay per QALYs was €60,000, SCS implantation would be cost-effective in 80% and 85% of cases, according to the NHS's and societal point of views, respectively.

4. Conclusions: Identifying signals for re-review

Table 2 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the conclusions of Spectrum Research, Inc. (SRI) with respect to the criteria that identify a trigger for an update.

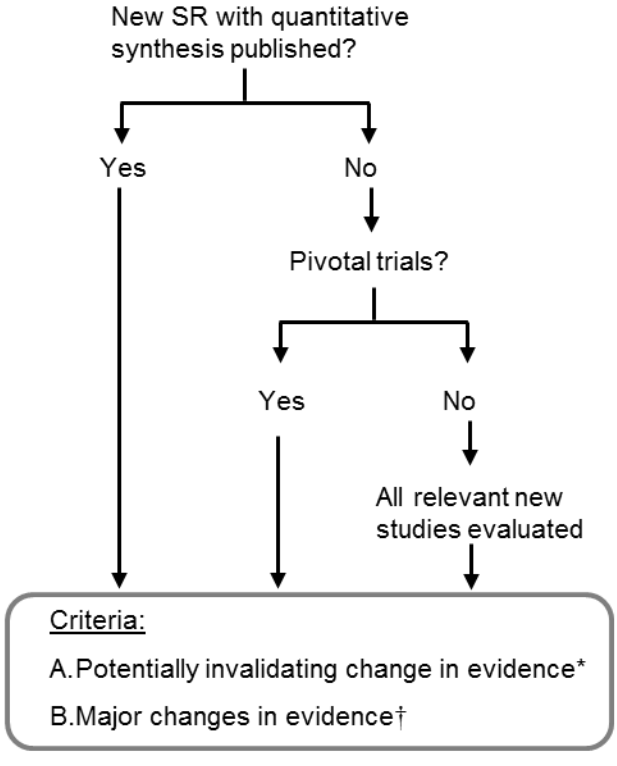
4.1 Key Question 1: With respect to efficacy, two studies compared SCS to conventional treatment in patients with diabetic neuropathy. Both found a short term pain improvement in favor SCS. There were no assessments of function or quality of life. Both studies report complications, some serious, to include 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) cross-over 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).

4.2 Key Question 2: 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

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

4.4 Key Question 4: 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).

Figure 1. Algorithm using a modified version of the Ottawa Method of identifying signals for SR updates



*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

Figure 2. Flow chart showing results of literature search

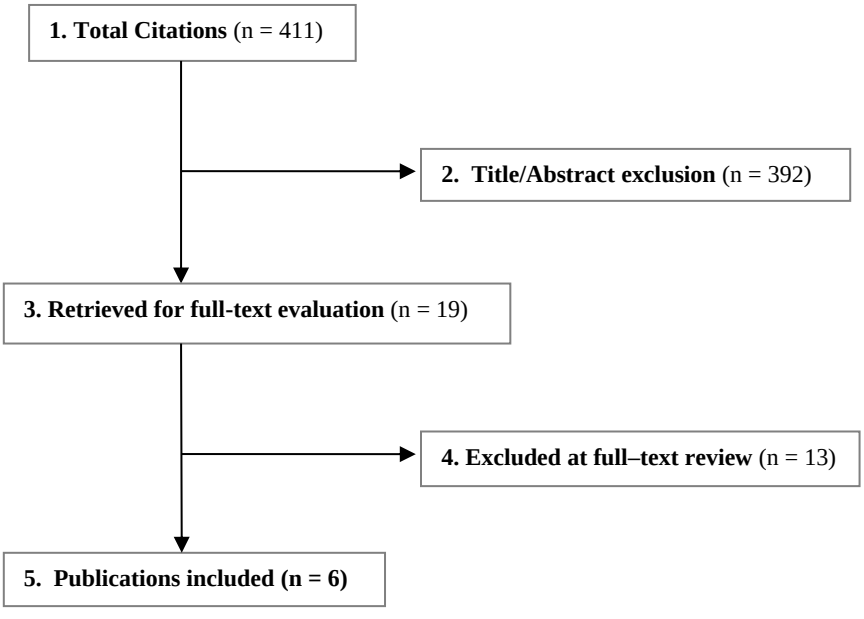


Table 1. Study characteristics of included studies

Author (Year) Study type	Demographics	Results	Conclusion	Limitations Conflict of interest
Schu (2013) cross-over RCT	N = 20 (all receiving conventional tonic SCS at time of enrollment) Male: 35% Age: 58.6 ±10.2 F/U: 1 week <u>Diagnosis</u>: FBSS <u>Intervention vs. control</u>: • Burst stim (5 pulses at 500 Hz, 40x/sec) vs. • Tonic stim (500 Hz) vs. • Placebo	<u>NRS pain intensity (0-10, 10 = worse pain):</u> • Burst Stim: 4.7 ±2.5 • 500-Hz Tonic Stim: 7.1 ±1.9 • Placebo Stim: 8.3 ±1.1 *p* <.05 burst vs. tonic, burst vs. placebo <u>Pain quality (SFMPQ):</u> • Burst Stim: 19.5 ±10.5 • 500-Hz Tonic Stim: 28.6 ±10.2 • Placebo Stim: 33.5 ±11.8 *p* <.05 burst vs. tonic, burst vs. placebo <u>Patient preference:</u> • Burst Stim: 80% • 500-Hz Tonic Stim: 10% • Placebo Stim: 0% • Conventional tonic Stim: 10% *p* = .0004 burst vs. tonic, burst vs. placebo, burst vs. conventional	Overall, burst stimulation resulted in significantly better pain relief and improved pain quality in the short term compared with 500-Hz tonic stimulation and placebo stimulation and was preferred by the majority of patients.	• Very short follow-up of only 1 week • No wash out period between cross-over • Trial aimed to compare effect of burst stimulation in patients with stable benefit from conventional SCS; may not be generalizable to patients naïve to stimulation Some authors are consultants for St. Jude Medical, Inc. receiving payment for educational presentations, some receive fellowship training or grants. St. Jude Medical, Inc. owns the rights to the burst SCS
De Ridder (2013) cross-over RCT	N = 15 Male: 27% Age: 54.1 (39-68, range) F/U: 1 week <u>Diagnosis</u>: FBSS (80%) Other (20%) <u>Intervention vs. control</u>: • Burst stim (5 pulses at 500 Hz, 40x/sec) vs. • Tonic stim (40-50 Hz) vs. • Placebo	<u>Axial, limb, general pain (%Δ from baseline, 0-100 mm):</u> • Burst Stim: 51.3%, 52.7%, 55.0% • Tonic Stim: 30.3%, 51.5%, 30.9% • Placebo Stim: 18.9%, 11.7%, 10.9% Axial: *p*<.05 burst vs. placebo Limb: *p* <.05 burst vs. placebo, tonic vs. placebo General: *p* <.05 burst vs. placebo, burst vs. tonic, tonic vs. placebo <u>PVAQ attention to pain, changes in pain:</u> • Burst Stim: 7.6%, 10.0% • Tonic Stim: 5.0%, 3.9% • Placebo Stim: 3.3%, 3.2% Attention to pain & to changes in pain: *p* <.05 burst vs. placebo, burst vs. tonic <u>Pain now, least pain, worst pain</u>	In comparison with placebo, burst, corrected for multiple comparisons, was significantly better for all measurements. The differences between tonic and burst stimulation are likely attributable to a more-selective modulation of the medial pain pathways by burst stimulation, as shown by the activation of the dorsal anterior cingulate cortex.	• Very short follow-up of only 1 week • No wash out period between cross-over • No description of random process • Trial aimed to compare effect of burst stimulation in patients with stable benefit from conventional SCS; may not be generalizable to patients naïve to stimulation Principle author holds a patent for burst stimulation

Author (Year) Study type	Demographics	Results	Conclusion	Limitations Conflict of interest
		• Burst Stim: 49.8%, 73.2%, 36.0% • Tonic Stim: 26.0%, 45.8%, 12.6% • Placebo Stim: 12.8%, 21.7%, 0.6% Pain now: p <.05 burst vs. placebo, tonic vs. placebo Least pain: p <.05 burst vs. placebo, tonic vs. placebo, burst vs. tonic Worst pain: p <.05 burst vs. placebo, burst vs. tonic		
Perruchoud (2013) cross-over RCT	N = 33* Male: 48% Age: 54.2 ±10.7 F/U: 2 weeks <u>Diagnosis</u>: Chronic LBP <u>Intervention vs. control</u>: • HFSCS (10,000 Hz) vs. • Placebo	<u>PGIC responders reporting at least "minimal improvement":</u> • HFSCS: 42.4% • Placebo Stim: 30.3% Mean benefit of HFSCS vs. placebo = 11.2% (95% CI: -10.1% to 32.5%), p = .30) <u>EQ-5D, VAS pain:</u> p >.05 for both	HFSCS was equivalent to placebo for all outcomes. 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.	• Very short follow-up of only 2 weeks • No wash out period between cross-over • Trial aimed to compare effect of HFSCS in patients with stable benefit from conventional SCS, may not be generalizable to patients naïve to stimulation. Funded and technical support for programming by Medtronic. Some authors consult for and are members of advisory boards for Medtronic, receiving consulting fees, honoraria, speaking and travel fees.
de Vos (2014) RCT	N = 60 Male: 63% Age: 59.5 ± 11.2 F/U: 6 months <u>Diagnosis:</u> Painful diabetic neuropathy (PDN) <u>Intervention vs. control</u>: • SCS (n = 40)	<u>Absolute VAS reduction over baseline</u> • SCS: 42 ± 31 • Control: 0 ± 20 p <.001 SCS vs. Control <u>Relative VAS reduction</u> • SCS: 55% ± 41% • Control: 0% ± 5% p <.001 SCS vs. Control <u>>50% pain reduction</u> • SCS: 60%	Overall, SCS reduces pain significantly and improves the quality of life in patients with refractory PDN in the lower extremities compared to conventional pain treatment.	• Random allocation concealment unclear • Open label design • Lack of placebo • No functional or quality of life outcomes One author received teaching fees from St. Jude Medical and is a paid consultant for Biolab Technology.

Author (Year) Study type	Demographics	Results	Conclusion	Limitations Conflict of interest
	• Conventional pain treatment (details NR) (n = 20)	• Control: 5% *p* <.001 SCS vs. Control Adverse events unrelated to procedure • SCS: 10% (4/40) • Control: 30% (6/20) Adverse events related to procedure† • SCS: 15% (6/40) • Control: 0%		
Slangen (2014) RCT	N = 36 Male: 67% Age 56.9 ±10.7 F/U: 6 months Diagnosis: Painful diabetic neuropathy (PDN) Intervention vs. control: • SCS +BMT (n = 22) • BMT alone) (n = 14)	>50% pain reduction (day, night) • SCS: 41%, 36% • Control: 0%, 7% *p* <.001, <.01 SCS vs. Control (day, night) PGIC for pain, for sleep • SCS: 55%, 36% • Control: 0%, 0% *p* <.001, <.01 SCS vs. Control (pain, sleep) Success‡ • SCS: 59% • Control: 7% *p* <.01 SCS vs. Control Adverse events unrelated to procedure • SCS: 10%§ • Control: 0%	Treatment success was shown in 59% of patients with painful diabetic peripheral neuropathy who were treated with SCS over a 6-month period, although this treatment is not without risks.	• Random allocation concealment unclear • Open label design • Lack of placebo • No functional or quality of life outcomes Funding from Medtronic who provided a grant for the employment of one of the investigators.
Zucco (2015) Cost effectiveness, cost utility using a before/after study design	N = 80 Male: 40% Age 58 ±13 F/U: 24 months Diagnosis: FBSS Intervention: SCS + CMM Comparator:	**Cost-effectiveness results (SCS + CMM versus CMM):** NHS perspective: • ICUR: €47,000/QALY • ICER: €3,222/NRS Society perspective: • ICUR: €38,372/QALY • ICER: €2,631/NRS	The cost-utility acceptability curve suggested that if decision makers' willingness to pay per QALYs was €60,000, SCS implantation would be cost-effective in 80% and 85% of cases, according to the NHS's and societal point of views, respectively	• Before – after study design • Pre SCS data collected retrospectively Funded by Medtronic Italy.

Author (Year) Study type	Demographics	Results	Conclusion	Limitations Conflict of interest
	CMM alone <u>Analysis</u>: • NHS and Society perspective • ICER, ICUR • Primary outcomes: Pain NRS for ICER, EQ-5D for ICUR			

Abbreviations: BMT: best medical therapy; CMM: conventional medical management; EQ-5D: EuroQol five dimensions questionnaire; FBSS: failed back surgery syndrome; F/U: follow-up; HFSCS: high frequency spinal cord stimulation; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; KQ: key question; LBP: Low back pain; NA: not applicable; NHS: National Health Service; NRS: Numerical rating scale; NS: not statistically significant; PGIC: Patient's Global Impression of Change; PVAQ: pain vigilance and awareness questionnaire; QALYs: Quality Adjusted Life Years; RCT: randomized controlled trial; SCS: spinal cord stimulation; SFMPQ: short form McGill Pain Questionnaire; VAS: visual analog scale

* Based on 33 of 38 patients randomized (87%).
† Adverse events included pain due to the implanted pulse generator in 2 patients and electrode lead migration in 1 patient. Two patients perceived incomplete overlap of the paresthesia with the painful area during trial stimulation, and they had a second electrode lead directly placed. There was
1 infection during trial stimulation, which was successfully resolved and followed by a permanent implantation. Finally, 1 patient turned out to have coagulopathy, which complicated the implantation procedure and prolonged hospitalization.
‡Success defined as ≥50% relief of pain intensity on an NRS for 4 days during daytime or nighttime or a score of ≥6 on a 7-point Likert scale (1 = very much worse and 7 = very much improved) of the PGIC scale for pain and sleep.
§Dural puncture during implantation of lead for test stimulation, followed by subdural hematoma and death (n=1); infection of the SCS system 6 weeks after implantation, slow but incomplete recovery (n=1).

Table 2. Spinal Cord Stimulation Summary Table

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
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 (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 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.	de Vos (2014)[2] Slangen (2014)[3] Schu (2013)[4] De Ridder (2013)[5] Perruchoud (2013)[6]	Two small industry sponsored RCTs compared SCS in patients with diabetic neuropathy to control treatments consisting of conventional or best medical therapy. [2,3] Each reported significant improvement in pain outcomes with SCS compared to controls at 6 months follow-up. No function or quality of life outcomes assessed, and no mid- or long-term follow-up results available. Three small industry sponsored cross-over RCTs compared either HFSCS or burst SCS to placebo stimulation. All had very short follow-up of 1 or 2 weeks. Two studies report significantly improved pain relief with burst SCS vs. placebo in patients with stable benefit from conventional SCS.[4,5] One study reports no difference in pain and quality of life outcomes comparing HFSCS with placebo stimulation.[6]	• New RCTs 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?			
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	de Vos (2014)[2] Slangen (2014)[3]	• Revision: 2/96 (2%) to include electrode repositioning or replacement • Other: 6/96 (6%) to include infection (n=2), pain from	• New studies do not invalidate the previous evidence (criteria A-2)

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
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** • 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.		pulse generator (n=2), incomplete overlap of paresthesia (n=1), coagulopathy (n=1) • Mortality: 1 (1%) from dural puncture during implantation of lead for test stimulation, followed by subdural hematoma and death	
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	None	None	• No new data

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
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 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. **7. Number of prior surgeries for pain** • There is moderate evidence from two cohort studies to suggest that the number of prior of operations for pain is not associated with pain relief (or success). One study additionally found no correlation between prior operations for pain and function/activity/medication usage at five years. **8. Pain location** • There is low evidence from four cohort studies that pain location does not affect outcomes. **9. Laterality of pain** • There is low evidence from one cohort study on FBSS patients with open workers' compensation claims that patients with unilateral pain have better pain relief and functional outcomes (as measured by the RDQ) at 12 months compared with patients with bilateral pain. **10. Allodynia or hypoesthesia at baseline** • There is low evidence from one cohort study that the presence of allodynia at			

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from SRI
baseline negatively correlates with success at one year, while the presence of hypoesthesia at baseline was not predictive of success. **11. McGill Pain Questionnaire** • There is conflicting evidence from two studies that the McGill Pain Questionnaire is associated with pain relief or success at follow-up with conflicting results. One study found an association between the evaluative subscale while the other study found no association with any subscale and outcome. **12. Minnesota Multiphasic Personality Inventory (MMPI)** • There is conflicting evidence from two studies that the MMPI is associated with pain relief or success at follow-up with conflicting results. One study found an association between the depression subscale while the other study found no association with any subscale and outcome. **13. SF-36 Mental Health scores** • There is low evidence from one cohort study on FBSS patients with open workers' compensation claims that patients with baseline SF-36 Mental Health scores in the top third have better pain relief and functional outcomes (as measured by the RDQ) at 12 months than do those patients who scored in the bottom third at baseline.			
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 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.	Zucco (2015)[7]	• Zucco et al. used a before-after study design to evaluate the cost-effectiveness and cost utility of SCS compared to conventional care in patients with FBSS. They report an ICUR: €47,000/QALY and ICER: €3,222/NRS. They conclude that if decision makers' willingness to pay per QALYs was €60,000, SCS implantation would be cost-effective in 80% and 85% of cases, according to the NHS's and societal point of views, respectively.	• 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).

References

1. Russo M, Van Buyten JP. 10-kHz High-Frequency SCS Therapy: A Clinical Summary. *Pain Med* 2015; **16**(5): 934-42.

2. de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain* 2014; **155**(11): 2426-31.

3. Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. *Diabetes Care* 2014; **37**(11): 3016-24.

4. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. *Neuromodulation* 2014; **17**(5): 443-50.

5. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. *World Neurosurg* 2013; **80**(5): 642-9 e1.

6. Perruchoud C, Eldabe S, Batterham AM, et al. Analgesic efficacy of high-frequency spinal cord stimulation: a randomized double-blind placebo-controlled study. *Neuromodulation* 2013; **16**(4): 363-9; discussion 9.

7. Zucco F, Ciampichini R, Lavano A, et al. Cost-Effectiveness and Cost-Utility Analysis of Spinal Cord Stimulation in Patients With Failed Back Surgery Syndrome: Results From the PRECISE Study. *Neuromodulation* 2015; **18**(4): 266-76; discussion 76.

Appendix A. Search Strategy and Electronic Databases

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

Search Strategy
(Aug 1, 2013 to Aug 25, 2016)
Limited to English language, human population

Database: 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
Cochrane Registry of Clinical Trials
EMBASE
PubMed

Appendix B. List of excluded articles after full-text review

Study	Reason for Exclusion:
Systematic reviews	
Bicket MC, Dunn RY, Ahmed SU. High-Frequency Spinal Cord Stimulation for Chronic Pain: Pre-Clinical Overview and Systematic Review of Controlled Trials. Pain Med 2016.	No quantitative synthesis
Cruccu G, Garcia-Larrea L, Hansson P, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. Eur J Neurol 2016.	No new RCTs included since previous report
Grider JS, Manchikanti L, Carayannopoulos A, et al. Effectiveness of Spinal Cord Stimulation in Chronic Spinal Pain: A Systematic Review. Pain Physician 2016; 19(1): E33-54.	No quantitative synthesis
Hou S, Kemp K, Grabois M. A Systematic Evaluation of Burst Spinal Cord Stimulation for Chronic Back and Limb Pain. Neuromodulation 2016; 19(4): 398-405.	No quantitative synthesis
Pope JE, Falowski S, Deer TR. Advanced waveforms and frequency with spinal cord stimulation: burst and high-frequency energy delivery. Expert Rev Med Devices 2015; 12(4): 431-7.	No quantitative synthesis
Russo M, Van Buyten JP. 10-kHz High-Frequency SCS Therapy: A Clinical Summary. Pain Med 2015; 16(5): 934-42.	No new RCTs included since previous report
Shamji MF, Westwick HJ, Heary RF. Complications related to the use of spinal cord stimulation for managing persistent postoperative neuropathic pain after lumbar spinal surgery. Neurosurg Focus 2015; 39(4): E15.	Narrative review
Verrills P, Sinclair C, Barnard A. A review of spinal cord stimulation systems for chronic pain. J Pain Res 2016; 9: 481-92.	No new RCTs included since previous report
RCTS	
Hayek SM, Veizi E, Hanes M. Treatment-Limiting Complications of Percutaneous Spinal Cord Stimulator Implants: A Review of Eight Years of Experience From an Academic Center Database. Neuromodulation 2015; 18(7): 603-8; discussion 8-9.	Retrospective study of an administrative database
Kapural L, Yu C, Doust MW, et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology 2015; 123(4): 851-60.	HFSCS vs. LFSCS, no non-SCS controls
Rigoard P, Desai MJ, North RB, et al. Spinal cord stimulation for predominant low back pain in failed back surgery syndrome: study protocol for an international multicenter randomized controlled trial (PROMISE study). Trials 2013; 14: 376.	Study protocol
Roulaud M, Durand-Zaleski I, Ingrand P, et al. Multicolumn spinal cord stimulation for significant low back pain in failed back surgery syndrome: design of a national, multicentre, randomized, controlled health economics trial (ESTIMET Study). Neurochirurgie 2015; 61 Suppl 1: S109-16.	Multicolumn vs. monocolumn stimulation. Awaiting publication of results.
Van Havenbergh T, Vancamp T, Van Looy P, Vanneste S, De Ridder D. Spinal cord stimulation for the treatment of chronic back pain patients: 500-Hz vs. 1000-Hz burst stimulation. Neuromodulation 2015; 18(1): 9-12; discussion	Comparing two modes of SCS, no non-SCS controls

Appendix C. Current comparative studies in ClinTrials.gov assessing SCS (accessed Aug 22, 2016)

NCT Number	Title	Conditions	Interventions	Control	Enrollment	Funded By	Start Date	Completion Date
NCT02514590	Wireless High Frequency Spinal Cord Stimulation for Chronic Pain	Back Pain	HFSCS	Conventional SCS	80	Industry	Mar-16	null
NCT01609972	Comparison of Senza to Commercial Spinal Cord Stimulation for the Treatment of Chronic Pain	Chronic LBP	HFSCS	Conventional SCS	356	Industry	Jun-12	Jun-15
NCT01923285	A Safety and Effectiveness Trial of Spinal Cord Stimulation of the Dorsal Root Ganglion for Chronic Lower Limb Pain	Chronic LBP	Dorsal root ganglion stimulation (AXIUM)	Conventional SCS	152	Industry	Aug-13	Dec-18
NCT01624740	High Rate Spinal Cord Stimulation (SCS) for Chronic Pain	Chronic Pain	High Rate Stimulation	Low Rate Stimulation	20	Industry	Jun-12	Dec-13
NCT02250469	A Randomised Pilot Study to Assess Differences in Stimulation Induced Paresthesia Between 2 Spinal Cord Stimulation Systems	Chronic Pain	Dorsal root ganglion stimulation (AXIUM)	Conventional SCS	34	Industry	Sep-14	May-17
NCT02093793	Safety and Effectiveness Study of the Precision SCS System Adapted for High-Rate Spinal Cord Stimulation	Chronic Pain, Back Pain	PRECISION SCS Adapted for High-Rate SCS	Conventional SCS	406	Industry	Mar-14	Oct-16
NCT02265848	High Frequency Stimulation Trials in Patients With Precision Spinal Cord Stimulator System	Chronic Pain, LBP, Radiculopathy, CRPS	HFSCS	Conventional SCS	22	Other	Oct-14	Jan-15
NCT01162993	Effect of Spinal Cord Stimulation (SCS) in Painful Diabetic Polyneuropathy	Diabetic Neuropathies, Pain,	Conventional SCS	Treatment as usual	40	Other	Apr-10	Jan-18
NCT01628237	Effectiveness and Cost Management of Multicolumn Spinal Cord Stimulation in Neuropathic Pain Patients With Failed Back Surgery Syndrome	FBSS	Multicolumn SCS	Monocolumn SCS	115	Other	May-12	Jan-15
NCT01697358	Spinal Cord Stimulation for Predominant Low Back Pain	FBSS, Back Pain, Leg pain	Conventional SCS	OMM	300	Industry	Jan-13	Apr-16
NCT02112474	The Pain Suppressive Effect of Alternative Spinal Cord Stimulation Frequencies	FBSS, Neuropathic Pain	High frequency SCS	Low frequency SCS	30	Other	Nov-14	Nov-16
NCT01486108	Burst Spinal Cord Stimulation for Neuropathic Pain	Neuropathic Pain	Burst SCS	Placebo, Tonic SCS	15	Other	Jan-11	Sep-11

CRPS: Complex Regional Pain Syndrome; FBSS: failed back surgery syndrome; HFSCS: high frequency spinal cord stimulation; LBP: low back pain; SCS: spinal cord stimulation;