WASHINGTON STATE HEALTH CARE AUTHORITY

HTA Report:
Spinal Cord Stimulation

Health Technology Assessment

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Health Technology Assessment Program
676 Woodland Square Loop SE
P.O. Box 42712
Olympia, WA 98504-2712
http://www.hta.hca.wa.gov

Spinal Cord Stimulation

Provided by:

Spectrum Research, Inc.

Final Report Prepared by:

Robin Hashimoto, PhD
Joseph R. Dettori, PhD, MPH
Nora B. Henrikson, PhD, MPH
Lisa Kercher PhD, MPH

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Introduction

Neuropathic pain is defined by International Association for the Study of Pain (IASP) as pain resulting from a primary lesion or dysfunction in the central or peripheral nervous system. Chronic neuropathic pain is likely underdiagnosed and undertreated, and its estimated prevalence has been reported to range from 1.5 to 8%. Underlying causes may include infection, trauma, compression of nerves, and surgery; an associated lesion may or may not be identifiable. Pain may be spontaneous or continuous; spontaneous pain may be manifested by stimuli which do not normally induce pain (termed "allodynia") such as gentle touch, patients may also experience a heightened response to stimuli that normally induce pain (termed "hyperalgesia"), such as hot or cold temperature. Clinical manifestations of neuropathic pain are different from non-nerve pain and may be described as pins and needles, electric shocks, intense stabbing pain, burning, tingling, and numbness; neuropathic pain may also be associated with itching, swelling, and temperature changes. Neuropathic pain is more likely to be chronic and less likely to respond to conventional medical treatment such as non-steroidal anti-inflammatory drugs than non-neuropathic pain. Neuropathic pain patients commonly experience a marked loss in quality of life.

Two of the most common types of chronic neurogenic pain treated with spinal cord stimulation include failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS). Patients with persistent back and/or leg pain following what appears to be successful spine surgery are diagnosed with failed back surgery syndrome (FBSS). Treatment of FBSS patients is difficult, as further surgery and conservative therapies typically do not relieve pain. FBSS has been estimated to affect approximately 30% of patients following lumbar spine surgery, though reported estimates range from 10 to 40%. Complex regional pain syndrome (CRPS) is a neuropathic pain disorder of unknown pathophysiology that affects one or more limbs. Most patients have a precipitating illness or injury that may or may not have been traumatic; the continued pain is disproportionate to the inciting event. The prevalence of CRPS type I was 20.57 per 100,000, and the incidence was 5.46 per 100,000 person years at risk based on one recent US-based population study.

The aim of treatment for chronic pain is to improve function and quality of life while relieving pain. Treating chronic neuropathic pain in general and FBSS and CRPS in particular is challenging, as the pain is often refractory to conservative therapies. Treatment of chronic neuropathic pain typically begins with a multidisciplinary approach using minimally invasive treatments, including physical therapy and rehabilitation, pharmaceutical pain management, and psychological therapy. For FBSS patients, reoperation may be employed. Spinal cord stimulation (SCS) is usually not considered as a treatment for neuropathic pain until conventional therapies have failed to provide adequate pain relief. It is typically used as a part of a multidisciplinary pain program in addition to conventional medical management, and treats rather than cures the chronic pain disorder. Potential benefits are pain relief, improved quality of life and functionality, as well as possible reduction in pain medication usage.

Although SCS has received FDA approval for the treatment of chronic back and limb pain, and a number of devices have been used both within and outside the U.S. for several years, questions remain regarding a number of important issues. When used in adult patients with chronic neuropathic pain who have failed alternative therapies,

1. What is the evidence of efficacy and effectiveness of spinal cord stimulation?
2. What is the evidence of safety of spinal cord stimulation?
3. What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub-populations?
4. What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

In light of the possible benefits of spinal cord stimulation, the potential impact of its use on health care costs and uncertainties regarding the evidence of effectiveness and safety in the short term and longer time horizons, patients, clinicians, and payers will benefit from a structured, systematic appraisal of the comparative effectiveness, safety, and economic impact of spinal cord stimulation. Thus, the objective of this Health Technology Assessment is to critically appraise and analyze research evidence on the effectiveness of and complications related to the use of spinal cord stimulation in patients with chronic neuropathic pain and to the extent possible, consider the potential financial impact.

Methods for evaluating comparative effectiveness

Spectrum Research, Inc.'s (SRI) method for technology assessment involves formal, structured systematic search of the peer-reviewed literature across a number of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments. Each included study is critically appraised using SRI's Level of Evidence (LoE) system which evaluates the methodological quality based on study design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the LoE with consideration of the number of studies and consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Throughout the process, SRI sought clinical review to assure that the clinical components are accurately represented and relevant. In addition, peer-review by clinical experts, health services researchers and those with expertise in economic and outcomes evaluation provide an assessment of the systematic review methodology, analyses and report conclusions.

Results

For key question 1, we identified a total of three RCTs and one prospective cohort study. One RCT included only patients with complex regional pain syndrome (CRPS-I); two RCTs included only patients with failed back surgery syndrome (FBSS). The prospective cohort study was conducted specifically on patients with open Washington state workers' compensation claims.

For key question 2, we identified six additional case series, all with mid-term follow-up. For key question 3, we identified four prospective and two retrospective cohort studies. We identified three cost-effectiveness analyses to address key question 4.

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

One RCT provided data on the short-term efficacy of SCS compared with physical therapy in complex regional pain syndrome (CRPS) patients. Two RCTs reported on the efficacy of SCS in patients with failed back surgery syndrome (FBSS): one RCT provided data on both the short- and mid-term efficacy of SCS and conventional medical management (CMM) compared with CMM alone, while another provided data on the short-term efficacy of SCS compared with lumbar reoperation. Heterogeneity between these studies prevented pooling of the data. In general, the RCTs reported significantly improved outcomes in the short-term for patients randomized to receive SCS than those randomized to the control groups; however, results were mixed at the mid-term follow-up in the one RCT reporting results after five years.

One prospective cohort study provided data on the short-term effectiveness of SCS compared with Pain Clinic and Usual Care treatments in FBSS patients with open workers' compensation claims in the State of Washington. In general, the cohort study found no differences in outcomes between patients in the SCS and two control groups.

"Success" from a composite score
Efficacy: One RCT found that patients randomized to receive SCS had significantly improved "success" (a composite of pain relief and patient satisfaction) compared with those randomized to undergo lumbar reoperation at mean of 2.9 years follow-up.

Effectiveness: The prospective cohort study on workers' compensation patients found no difference between SCS, pain clinic (PC), or usual care (UC) groups at any follow-up up to 24 months in the percent of patients achieving the primary outcome composite measure of success (includes pain, function, and medication usage components).

Pain relief
Efficacy: Patients randomized to receive SCS had significantly improved pain relief compared with those randomized to undergo control treatments in two RCTs with ≤ 2 year follow-up. One of these RCTs reported that the differences between groups in both the change in VAS scores (from baseline) and in mean VAS scores were no longer statistically significant by three to five years post-implantation.

Effectiveness: The prospective cohort study on workers' compensation patients reported that significantly more patients in the SCS group achieved ≥ 50% leg pain relief by six months than those in the UC group, there was no difference between the SCS and PC group at the same follow-up; furthermore, no differences were identified between groups in the percentage of patients achieving leg pain relief of ≥ 50% or more at the 12- and 24-month follow-ups.

Function

Efficacy: One RCT found that patients in the SCS group had significantly better Oswestry Disability Index scores than those in the CMM group at six months follow-up. Another RCT reported no significant differences between the SCS and reoperation groups in the neurological status or ability to perform daily activities a mean of 2.9 years follow-up, however, raw data were not provided.

Effectiveness: There were no significant differences in either the Roland-Morris Disability Questionnaire (RDQ) scores or ability to perform daily tasks between treatment groups in the prospective cohort study on workers' compensation patients.

Health-related quality of life (HR-QoL)

Efficacy: One RCT reported no difference in several QoL outcome measures between the SCS and physical therapy groups, including the mean percent change in quality of life at the 6- and 24- month follow-ups as well as the Nottingham Health Profile, EQ-5D (EuroQol-5D), and Self-Rating Depression Scale scores at five years. Another RCT reported that patients randomized to receive SCS had significantly better scores in seven of the eight SF-36 (Short-Form 36) outcome scales compared with those randomized to receive CMM at six months. The same RCT reported that the six-month EQ-5D utility scores were significantly better in the SCS compared with the CMM group. Further, no difference was found between groups in the rate of patients (not working at baseline) who had returned to work by six months.

Effectiveness: The prospective cohort study on workers' compensation patients reported no significant differences between treatment groups in SF-36 scores and work/disability status.

Patient satisfaction and perceived effect

Efficacy: One RCT reported that significantly more patients in the SCS group were satisfied with both their level of pain relief and with their treatment in general than those in the CMM group at six months follow-up. Another RCT incorporated patient satisfaction with pain relief into a composite outcome, "success", which was reported above. Another RCT reported global perceived effect (GPE) scores. Significantly more patients in the SCS group reported GPE of "much improved" or "best ever" at both the 6- and 24- month follow-ups compared with the physical therapy group; however the differences between groups were no longer statistically significant by five years.

Medication usage

Efficacy: One RCT reported no differences at six months between the SCS and CMM groups in the percentage of patients using opioids, non-steroidal anti-inflammatory medications, or antidepressants; however, significantly fewer SCS patients were taking anticonvulsants than those in the CMM group. There were no differences between the SCS and CMM groups in the percentage of patients using all reported non-drug therapies (eg., physical or psychological rehabilitation, acupuncture, or massage) except for TENS (transcutaneous electrical nerve stimulation), for which the rate of use was lower in SCS compared with CMM patients. Another RCT found that significantly more patients in the SCS group were taking a stable or decreased

dosage of opioids (versus baseline) than those in the reoperation group at a mean of 2.9 years follow-up.

Effectiveness: Although significantly fewer patients in the SCS group used opioids on a less than daily basis than did those in the PC group at six months, no other significant differences between treatment groups were identified in the prospective cohort study on workers' compensation patients.

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

Short-term (< 5 years) safety data were reported by three RCTs and one prospective cohort study; mid-term (5–10 years) safety data were reported by one RCT and six case series. No long-term safety data were available.

Revision
All three RCTs and the one cohort study reported short-term revision rates of SCS devices; one RCT and all six case series reported mid-term revision rates. However, each study reported the data differently, and not all studies reported an overall revision rate (the proportion of patients with one or more revision). Therefore, revision rates were difficult to pool. Reasons for revision included (but were not limited to): revision or replacement of electrodes/leads due to migration, improvement of paresthesia, defective electrodes, infection, fractured electrode, or hardware malfunction; revision or replacement of generators (or stimulators) due to painful pulse generator pockets, migration, battery depletion, defective generator, electrical leak, or failure; revision of the connecting cable/lead due to fracture, discomfort, or insulation damage; SCS systems were explanted (and often reimplanted) due to infection, recurrent rejection, discomfort, ineffective pain relief, new intolerable pain, defective transmitters, or seizures.

Other SCS-related complications or side effects
Complications or side effects ascribed to the SCS device were reported by two RCTs, one cohort study, and six case series; overall short-term rates ranged from 8–100% of patients. At two years follow-up, one RCT reported that side effects had occurred in 100% of available SCS patient; another RCT reported device-related complications not requiring revision in 14% of patients. Complications or side effects ascribed to the SCS system included: change in amplitude by bodily movements, paresthesia in other body parts, pain or irritation from pulse generator, disturbed urination, movements or cramps resulting from elevated amplitute, infection, loss of therapeutic effect, loss of parasthesia, or unpleasant paresthesia, subcutaneous hematoma, cerebrospinal fluid leak, dural puncture, or pain over SCS components.

Complications not related to SCS
Complications not related to SCS were reported by one RCT. Rates of new illness, injury, or condition and of worsening of the pre-existing condition were similar for both the SCS and the CMM group; however the percentage of patients that had experienced drug adverse events or extra pain events were 15 to 23% higher in the CMM group than in the SCS group at one year.

Mortality
Short-term mortality data were obtained from three RCTs and one prospective cohort study. Two deaths occurred in the SCS groups (2/139); one due to a sudden cardiac event at six months and another between six and twelve months for which the cause was not reported. No deaths occurred in any of the control groups (0/179). Mid-term mortality data were obtained from one RCT and three case-series. Two deaths occurred in SCS patients; one due to cerebrovascular accident in a patient being treated for angina, not neuropathic pain, and another due to suicide. No deaths were attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.

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

We identified six small prognostic studies (four prospective and two retrospective studies). In general, very little evidence was found that suggests that any of the factors evaluated were associated with differential outcome following SCS. Prognostic factors evaluated included:

Age
Three studies evaluated whether age had an effect on pain relief in the first year following implantation. While one study reported that younger age was significantly associated with improved pain relief, two other studies found no association between patient age and pain relief. Furthermore, one prospective cohort study demonstrated that age was not correlated with SF-36 or GPE scores at nine months

Sex
Four studies evaluated the effect of patient sex on pain relief following SCS. Three studies found that sex was not predictive of pain relief in the first year, and one study reported that success at five years was significantly higher in females. This study also reported that females had significant improvements in a combination of everyday activities (ability to work, walk, climb stairs, sleep, have sex, drive, and eat), neurological function (strength, sensation, and bladder/bowel control), and medication use. One other study found no correlation between patient sex and SF-36 or GPE scores at nine months.

Workers' compensation or other disability payments
One study found no difference in the percentage of patients who achieved at least 50% pain relief at three months between those receiving workers' compensation or other disability payments than those not under such programs.

Duration of pain
Two studies evaluated and found no relationship between duration of chronic pain and pain relief in the first year following SCS implantation. One study reported that CRPS patients with a longer duration of chronic pain had significant improvements in quality of life at nine months as

measured by two (of eight) domains of the SF-36 outcome measure by multivariate analysis; however, no association was found between pain duration and GPE scores.

Pain intensity
One study evaluated and found no association between the pain intensity at baseline and pain relief at one year.

Time since first lumbar surgery
One study found that the time since the first lumbar surgery was not associated with success or a composite score that included everyday activities, neurological function, and medication use at five years.

Number of prior operations for pain
Two studies evaluated and found no association between the number of previous operations for chronic pain and pain relief at three months or success at five years.

Pain location
Four studies evaluated and found no association between pain location and pain relief at follow-up, though each study compared different locations. One study reported no association between hand versus foot pain with nine-month SF-36 or GPE scores; another study found no difference in a combination of everyday activities, neurological function, and medication use between patients with axial versus radicular pain.

Laterality of pain
One study suggested that more SCS patients with unilateral pain achieved leg pain relief of at least 50% than did those patients with bilateral pain; similarly, more patients with unilateral pain had functional improvement (as measured by the RDQ) compared with those patients with bilateral pain.

Allodynia or hyposthesia at baseline
One retrospective study demonstrated that the absence of brush-evoked allodynia at baseline was significantly associated with success at one-year. In contrast, the presence of mechanical hypoesthesia at baseline was not correlated with success.

McGill Pain Questionnaire
Two studies evaluated the predictive effect of baseline McGill Pain Questionnaire scores with conflicting results. While one study found that higher McGill evaluative subscores were associated with improved pain relief, the other study found that none of the domains of the McGill Pain Questionnaire were predictive of success at five years.

Minnesota Multiphasic Personality Inventory (MMPI)
Two studies evaluated whether MMPI scores at baseline were associated with improved pain relief. One study found that lower scores for the depression subscale were significantly correlated with pain relief at three months, while the other study found no correlation between MMPI scores and pain relief at a mean of 3.5 years.

SF-36 Mental Health Component
One study found that SCS patients with baseline SF-36 Mental Health scores in the top third of patients had better pain relief and functional outcomes (as measured by the RDQ) compared with those patients with baseline scores in the lowest third.

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

We included three complete economic evaluations; two were published economic evaluations of SCS compared with other interventions for pain and one was included as part of the recent HTA conducted by NICE in the UK. 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 reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) 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.

Summary

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

SCS	Strength of evidence	Conclusions/Comments
1. Efficacy (Short-term: < 5 years)	**Moderate**	• **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 reoperation) 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 o 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).
	Low	• **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.
(Mid-term: 5 to < 10 years)	**Low**	• **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.
(Long-term: ≥ 10 years)	**No evidence**	• There are no data available to assess long-term efficacy.
2. Effectiveness (Short-term: < 5 years)	**Low**	• **Composite measure 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 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.
(Mid & Long-term: ≥ 5 years)	**No evidence**	• There are no data available to assess mid- or long-term effectiveness.

NA: not applicable

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

SCS	Strength of evidence	Conclusions/Comments
1. Revision	**High**	• 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	**Moderate**	• 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	**High**	• 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, one as a result of suicide. 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, and the cause of one was not reported. No death was attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.

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

SCS	Strength of evidence	Conclusions/Comments
Summary: **There is no moderate or high evidence that any of the factors or subpopulations evaluated were associated with outcome following SCS.**		
1. Age	**Low**	• 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	**Low**	• There is mixed results 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	**Low**	• 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	**Moderate**	• 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.
ad5. Pain intensity	**Low**	• 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	**Low**	• 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	**Moderate**	• 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	**Low**	• There is low evidence from four cohort studies that pain location does not affect outcomes.
9. Laterality of pain	**Low**	• 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	**Low**	• There is low evidence from one cohort study that the presence of allodynia at baseline negatively correlates with success at one year, while the presence of hypoesthesia at baseline was not predictive of success.
11. McGill Pain Questionnaire	**Low**	• 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)	**Low**	• 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	**Low**	• 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 stimulators?

	Strength of evidence	**Conclusions/Comments**
Cost-effectiveness	**Moderate**	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 reoperation 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 reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) 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.

1. Appraisal

1.1. Rationale

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 cases, reoperation. SCS is typically used as a part of a multidisciplinary pain program in addition to conventional medical management, and treats rather than cures the chronic pain disorder. Potential benefits are pain relief, improved quality of life and functionality, as well as possible reduction in pain medication usage. Furthermore, implantation of SCS components is minimally invasive and is fully reversible. To increase the likelihood of success, patients typically undergo a trial period of stimulation before having the device permanently implanted.

Although SCS was developed over four decades ago, it was not used for many years due to ineffective pain relief. In the last decade, SCS has resurfaced as a potential treatment for chronic pain. Improved understanding of the relevant indications and design of the components of a SCS system have led to better outcomes. However, questions remain about the efficacy and effectiveness of SCS both in the short and the long term; the rates of complications arising from their implantation and use; and the appropriate patient selection criteria (e.g., age, gender, workers' compensation, history of pain, etc.).

1.2. Key Questions

Key questions are developed by the Washington State Health Technology Assessment Program.

When used in adult patients with chronic neuropathic pain who have failed alternative therapies:

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

a. Short-term and long-term outcomes
b. Impact on pain, function, and quality of life
c. Other reported measures including: use of pain medications and opioids, return to work; intensity and duration of use

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

a. Adverse events type and frequency (mortality, major morbidity, other)
b. Revision and removal rates including loss of paresthesia (if not addressed in efficacy)
c. Infections
d. Lead migration
e. Technical malfunctions (e.g., early battery failure, broken leads)

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

a. Gender
b. Age
c. Psychological or psychosocial co-morbidities
d. Diagnosis or pain type
e. Other patient characteristics or evidence based patient selection criteria
f. Provider type, setting or other provider characteristics
g. Health care system type, including worker's compensation, Medicaid, state employees

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

a. Costs (direct and indirect) in short term and over expected duration of use
b. Replacement

1.3. Outcomes Assessed

Because spinal cord stimulation is used as a treatment for chronic pain, the primary and most commonly reported outcome was pain relief. Typically, pain was reported by patients on a 0 to 10 cm VAS (visual analogue scale), with 0 cm indicating no pain and 10 cm indicating worst pain imaginable. Many studies report the percentage of patients that achieved 50% pain relief compared to baseline, while others reported the difference in pain intensity that occurred from treatment. Some studies reported the composite outcome of "success" as the primary outcome. Varying definitions were used, but "success" always included pain relief as one of its components; other components included patient satisfaction, function, and medication usage. Specific definitions are detailed in the results section as appropriate. Studies reported secondary outcomes that included patient satisfaction, global perceived effect (GPE), health-related quality of life outcome measures (EQ-5D, SF-36, Nottingham Health Profile, Self-Rating Depression Scale scores), function (Oswestry Disability Index, Roland-Morris Disability Questionnaire), and medication usage. Further details on the outcome measures used can be found in Table 4.

2. Background

2.1. The condition: chronic neuropathic pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with [or described in terms of] actual or potential tissue damage"[1]. The IASP emphasizes that pain is a psychological response that may or may not be triggered by a physical stimulus, and that the experience of pain is subjective. Pain that persists for several months or for longer than anticipated is referred to as chronic pain. Chronic pain can result from an ongoing or past physical cause, but may also occur in the absence of any physical injury[2]. In addition to the pain itself, chronic pain patients may experience accompanying physical and emotional symptoms such as limited mobility, tense muscles, low energy, appetite and sleep changes, as well as depression and anxiety. Together, these symptoms may dramatically affect a person's quality of life and ability to work or perform other activities[3].

Neuropathic pain is defined by the IASP as pain resulting from a primary lesion or dysfunction in the central or peripheral nervous system[1]. Clinical manifestations of neuropathic pain are different from non-nerve pain and may be described as pins and needles, electric shocks, intense stabbing pain, burning, tingling, and numbness; neuropathic pain may also be associated with itching, swelling, and temperature changes[4, 5]. Pain may be spontaneous or continuous[6]. Neuropathic pain is more likely to be chronic and less likely to respond to conventional medical treatment such as non-steroidal anti-inflammatory drugs than non-neuropathic pain[7, 8]. Neuropathic pain can be distinguished from other types of pain by the following characteristics: (1) pain and sensory symptoms that last longer than the expected healing period; (2) the presence of negative and/or positive sensory phenomena; and (3) the presence of other neurological symptoms including autonomic and motor phenomena[8]. Underlying causes may include infection, trauma, compression of nerves, and surgery; an associated lesion may or may not be identifiable[9]. Further, spontaneous pain can be manifested in neuropathic pain patients by stimuli which do not normally induce pain (termed "allodynia")[1], such as the wind or gentle touch by clothing, foam brush, or cotton swab; patients may also experience a heightened response to stimuli that normally induce pain (termed "hyperalgesia")[1], such as hot or cold temperature[9]. Neuropathic pain patients commonly experience a marked loss in quality of life[6].

Chronic neuropathic pain is likely underdiagnosed and undertreated, and its estimated prevalence has been reported to range from 1.5 to 8%[7, 10]. Diagnoses of peripheral neuropathic pain include complex regional pain syndrome (CRPS), carpal tunnel syndrome, diabetic neuropathy, phantom limb pain, postherpetic neuralgia, radiculopathy, and post-traumatic neuralgias; diagnoses of central neuropathic pain include multiple sclerosis-related pain, poststroke pain, and posttraumatic spinal cord injury pain[9]. Patients with persistent back and/or leg pain following what appears to be successful spine surgery are diagnosed with failed back surgery syndrome (FBSS)[5]. In the studies that met our inclusion criteria, the use of spinal cord stimulation was most commonly evaluated in patients with FBSS (with leg pain meeting or exceeding back pain) and complex regional pain syndrome (CRPS).

2.2. Failed back surgery syndrome (FBSS)

Failed back surgery syndrome (FBSS) is a generalized disorder that is characterized by chronic pain in the lower back and/or legs that persists or recurs following anatomically successful spinal surgery[11, 12]. There is no equivalent to FBSS following other types of surgery[4]. Treatment of FBSS patients is difficult, as further surgery and conservative therapies typically do not relieve pain[11]. FBSS has been estimated to affect approximately 30% of patients following lumbar spine surgery, though reported estimates range from 10 to 40%[12-14]

2.3. Complex regional pain syndrome (CRPS)

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy (RSD) or causalgia, is a neuropathic pain disorder that affects one or more limbs. Although the pathophysiology is not known, most patients have a precipitating illness or injury. IASP diagnostic criteria for CRPS include (1) pain that develops after a precipitating event that may or may not have been traumatic; (2) continuing pain, allodynia, and hyperalgesia, that is disproportionate to the inciting event; (3) presence or history of edema, abnormal blood flow, or sudomotor abnormalities in the affected region; and (4) no other comorbid conditions that may account for the pain. CRPS can be classified into two types, which are identical except that CRPS type II requires that the presence of a major peripheral nerve injury while CRPS type I does not require the presence of an identifiable nerve lesion[15, 16]. CRPS patients typically describe their pain as burning, pricking, aching, and shooting; allodynia and hyperalgesia are also hallmarks of this disorder and may be severe. Typically, the pain affects beyond the area of the initial injury and may affect the contralateral limb[16]. CRPS tends to affect younger patients (mean age ranging from 36 to 46 years) and is more common in women[16, 17]. In addition, the upper limb tends to be affected more commonly than the lower limb[17]. The responsiveness of CRPS to treatment improves with early diagnosis[15, 16]. The prevalence of CRPS type I was 20.57 per 100,000, and the incidence was 5.46 per 100,000 person years at risk based on one recent US-based population study[17].

2.4. The technology and its comparators

The aim of treatment for chronic pain is to improve function and quality of life while relieving pain. Treating chronic neuropathic pain in general and FBSS and CRPS in particular is challenging, as the pain is often refractory to conservative therapies[7, 11, 16].

After identifying the underlying cause of pain, treatment of chronic neuropathic pain typically begins with a multidisciplinary approach using minimally invasive treatments, including physical therapy and rehabilitation, pharmaceutical pain management, and psychological therapy. For FBSS patients, reoperation may be employed. Patients with inadequate responses to minimally invasive therapies may subsequently be treated with more invasive therapies, which may include intrathecal drug therapy, epidural or catheter blocks, or spinal cord stimulation.

Comparators
Treatment for neuropathic pain is multidimensional and patient-specific. Therapies may include the following[9, 18, 19]:

Disease-specific interventions such as nerve root decompression or reoperation

Pharmacological management may include opioid analgesics, non-steriodal anti-inflammatory drugs (NSAIDs), anticonvulsants, corticosteroids, antidepressants, and/or anti-anxiety medications. Topical medications such as a 5% lidocaine patch or capsaicin may also be used. First-line medications may include gabapentin, a 5% lidocaine patch, opioids, tramadol hydrochloride, and tricyclic antidepressants, as these have demonstrated efficacy in randomized contolled trials[9]. In general, drug-related adverse events are common, especially in elderly patients who are more likely to be taking other medications. The types of and intensity of side effects may be different for each patient and vary; adverse effects may include dizziness, edema, nausea, cognitive impairment, constipation, sedation, hypotension, hypertension, seizures, cardiac events in those with a history of cardiovascular disease, weight gain, substance tolerance, substance dependence, and substance abuse.

Physical rehabilitation including physical therapy, range-of motion exercises, manipulation, splinting, assistive devices, ergonomic methods

Behavioral and psychological therapies may include psychological counseling, cognitive-behavioral therapy, hypnosis, guided imagery

Stimulation-based therapies such as acupuncture, transcutaneous nerve electrical stimulation (TENS), massage

Regional anesthetics may be considered after less-invasive treatments have failed to provide adequate pain relief, and may include sympathetic blocks, epidural/intrathecal blocks, selective nerve root blocks, and epidural/intrathecal pumps

Spinal cord stimulation
Spinal cord stimulation (SCS) is usually not considered as a treatment for neuropathic pain until conventional therapies have failed to provide adequate pain relief. It is typically used in addition to other therapies for pain (conventional medical management), and treats rather than cures the chronic pain disorder. Potential benefits are pain relief, improved quality of life and functionality, as well as possible reduction in pain medication usage.

History and mechanism of action
SCS was first developed over forty years ago by Shealy et al[20] based on Melzack and Wall's gate-control theory[21]. According to the gate-control theory of pain, nociceptive signals from the stimulatory peripheral nerves could be interrupted by activity of the large-diameter myelinated primary afferent fibers. Because activity in large afferents was postulated to inhibit activity of neurons in the dorsal horn, stimulation of the large afferents would thus

inhibit the transmission of pain signals to the brain[22, 23]. Early use of spinal cord stimulation, then called dorsal column stimulation, was quite limited and associated with poor outcomes. In the last decade, SCS has resurfaced as a potential treatment for chronic pain. Improved understanding of the relevant indications and design of the components of a SCS system have led to better outcomes.

The mechanism by which SCS mediates its pain-relieving effects is not fully understood. Recent research has suggested that SCS may primarily reduce continuous and evoked pain, particularly allodynic pain, but whether SCS affects sensations of acute pain remains controversial. It has been suggested that SCS inhibits pain by acting on segmental spinal levels[24]. Possible mechanisms of action may include enhancing the release of GABA (gamma-aminobutyric acid) and adenosine in the dorsal horn, the levels of which are typically low in patients with allodynic pain, and both of which seem to have a potentiating effect of SCS; inhibiting the release of the excitatory amino acids glutamate and aspartate; and possibily increasing the release of serotonin and substance P and peripheral blood flow[22, 24]. Furthermore, MRI studies in humans showed that SCS induced activity in the somatosensory cortex and the cingulated gyri, which are linked to processing the somatosensory and affective components of pain[22]. In addition, most agree than pain may be masked by the tingling and vibratory sensations of paresthesia, which occur with dorsal column stimulation, as successful pain reduction is dependent on complete overlap of the paresthesia with the painful region[23]. Further research is necessary to fully understand the mode of action by which SCS inhibits neuropathic pain.

SCS systems: components and implantation

Spinal cord stimulators consist of four components:

- An implantable pulse generator (IPG) with a rechargeable or a non-rechargeable battery; the generator can have a single- or dual output(s), and is typically implanted under the skin in the abdominal or buttock region; the power source may be internal or external,
- A lead extension cable, which connects the IPG to the lead
- Leads with one or more electrode contacts in the spinal cord region (typically there are four or eight contacts per lead), and
- A remote control hand-held programmer that allows the patient to control the IPG output parameters and additionally receives feedback from the IPG. Clinicians set individualized output stimulation parameters for each patient, and the patient uses the programmer to select these pre-set parameters.

Implantation of SCS components is fully reversible. Typically, patients undergo a 3–14 day trial stimulation to determine whether they can achieve adequate pain relief as well as tolerate the parasthesia sensation produced by the electrical stimulation. Criteria for a successful trial stimulation vary, but commonly require pain relief of at least 50% and improved function[13, 14, 22, 25]. Trial stimulation involves implantation of the percutaneous electrode lead in the epidural space such that the leads reach the dorsal column of the spinal cord to affect its pain transmission. Leads are placed in a region that should correspond to the painful area: for CRPS patients, electrodes may be placed with the tip generally in the C4 and T12 regions for hand and foot pain, respectively[25], while FBSS patients may have electrodes

implanted in the T8-T10 levels of the spinal cord[22]. Placement of the leads may vary slightly by patient, and correct positioning is critical because overlap of the paresthesia with the painful area is necessary for adequate pain reduction[22]. Electrode placement is performed under light anesthesia, as it is typically inserted into the epidural space using a needle. The lead is connected to an external stimulator device, and patients are commonly awakened in order to determine whether the electrode position provides adequate paresthesia overlap with the painful area.

Permanent SCS implantation takes place in those patients who had successful trial stimulations. This procedure may utilize the lead already in place from the trial stimulation, although this approach requires that the lead be surgically anchored during trial, making the trial more invasive. Alternatively the trial lead is removed and a permanent lead is implanted, most commonly via needle insertion, though laminectomy is sometimes used. A subcutaneous pocket is created in the lower abdominal or buttock area for the implantable pulse generator, which is connected to the lead by the lead connection which is anchored under the skin[22]. Implantation is done on an outpatient basis; discomfort usually lasts for a week or two following surgery, and strenuous activities will be restricted for two or three months.

The longevity of the SCS systems and batteries will vary with patient pain patterns, the level of stimulation required, and whether a single- or dual-lead system is used. Reoperation may be necessary to replace the battery (although many current systems utilize rechargeable batteries which could decrease or eliminate this need for revision), reposition the lead or generator, replace failed components, or remove (and subsequently re-implant) the system due to infection[22], due to component failures or lead position.

Indications for use[26-28]

In the US, a number of spinal cord stimulator systems have been approved by the FDA for treatment of chronic intractable pain in the trunk and/or limbs including unilateral or bilateral pain associated with FBSS and intractable low back pain and leg pain, and for some devices, CRPS, radicular pain syndrome or radiculopathies resulting in pain secondary to FBSS, post-laminectomy pain, unsuccessful disc surgery, degenerative disc disease or herniated disc pain refractor to conservative and surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, and multiple back surgeries. Each potential patient should undergo a period of trial stimulation before having an SCS device permanently implanted. We identified three manufacturers with FDA-approval for SCS devices; the devices currently listed on their company websites are as follows:

- Boston Scientific (Natick, Massachusetts): Precision Plus SCS system (rechargeable system)
- Advanced Neuromodulation Systems (St. Jude Medical, Plano, Texas): Eon, Eon Mini rechargeable systems; Genesis, EonC conventional systems with non-rechargeable batteries inside the generator; Renew system with an external power sources
- Medtronic: RestoreUltra, RestoreAdvanced Neurostimulators (rechargeable battery); PrimeAdvanced Neurostimulator (non-rechargeable battery)

Contraindications[26-28]

Patients should not receive permanent SCS therapy who:

- failed trial stimulation due to ineffective pain relief
- are poor surgical risks
- are pregnant
- are unable to operate the SCS system
- have cardiac pacemakers (unless specific precautions are taken regarding the mode and frequency of the device and not contraindicated for the particular device)
- have cardioverter defibrillators
- have active general infections
- have multiple illnesses

Additionally, SCS systems must be removed prior to diathermy or (depending on the device) exposure to any source of strong electromagnetic interference such as MRI (magnetic resonance imaging), therapeutic ultrasound, or defibrillation. Further, patients should turn the devices off prior to operating heavy machinery or power tools to avoid over-stimulation[26-28].

2.5. Clinical Guidelines

National Guideline Clearinghouse

A search of the National Guidelines Clearinghouse for "spinal cord stimulation" retrieved 36 guidelines, seven of which provided specific guidance for the use of spinal cord stimulation (SCS) devices for neuropathic pain. Two additional guidelines were identified in the public responses to the draft of this report. All nine guidelines are summarized chronologically below:

Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists task force on chronic pain management and the American Society of Regional Anesthesia and Pain Medicine (2010)[29]

The organizational members and consultants "strongly agree" that SCS should be used for persistent radicular pain, and all agree that it should be used for other conditions, such as postherpetic neuralgia, postamputation pain, peripheral neuropathic pain, spinal cord injury, CRPS, cauda equina syndrome, and cervical root injury pain. In addition, all members and consultants "strongly agree" that a SCS trial should be performed prior to considering permanent implantation of a stimulation device[29].

Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society (2009)[30]

The American Pain Society recommends that, for the treatment of persistent and disabling radicular pain following surgery for herniated disc (with no evidence of a persistently compressed nerve root), clinicians discuss the risks and benefits of SCS as a treatment option, and note the high rate of complications following SCS implantation. This recommendation was

classified as weak (benefits and risks and burdens are finely balanced) and based on moderate-quality evidence[30].

Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain (2009)[31]

The recommendation for clinical use of SCS for FBSS on a long-term basis is 1B or 1C, indicating a strong recommendation in which the benefits clearly outweigh the risk and burdens[31].

Institute for Clinical Systems Improvement (ICSI): Assessment and management of chronic pain (2008)[18]

Regarding treatment of chronic pain, the ICSI[18] considers placement of a SCS to be a level II treatment, which is only considered appropriate in patients who have failed more conservative (level I) treatment options (including transcutaneous nerve stimulation, drug therapies, physical rehabilitation, and behavioral techniques). SCS should be performed alongside a comprehensive treatment plan that includes pharmacologic, rehabilitative, and psychological interventions; if used alone, the evidence is limited in its success.

National Institute for Health and Clinical Excellence (NICE) appraisal guidance: Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (2008)

NICE provides guidance to the NHS (National Health Services) for England, Wales, Northern Ireland, and Scotland. Guidelines regarding the use of SCS for the treatment of neuropathic pain is summarized as follows[19]:

SCS is recommended as a treatment option for adults with chronic pain of neuropathic origin who continue to experience chronic pain of at least 50mm on a 0–100mm VAS for at least six months despite appropriate conventional medical management, and who have had a successful trial of stimulation.

SCS should be provided only after an assessment by a multidisciplinary team experienced in chronic pain assessment and management of people with spinal cord stimulation devices, including experience in the provision of ongoing monitoring and support of the person assessed.

When assessing the severity of pain and the trial of stimulation, the multidisciplinary team should be aware of the need to ensure equality of access to treatment with SCS. Tests to assess pain and response to SCS should take into account a person's disabilities (such as physical or sensory disabilities), or linguistic or other communication difficulties, and may need to be adapted.

If different SCS systems are considered to be equally suitable for a person, the least costly should be used. Assessment of cost should take into account acquisition costs, the anticipated longevity of the system, the stimulation requirements of the person with chronic pain and the support package offered.

American College of Occupational and Environmental Medicine (2007): Low back disorders- occupational medicine practice guidelines[32]

The use of SCS for acute, subacute, or chronic low back pain; radicular pain syndromes; or FBSS is not recommended based on insufficient evidence for an evidence-based recommendation due to high costs or high potential for harm to the patient (Evidence Rating I: insufficient or irreconcilable evidence)[32].

European Federation of Neurological Societies (EFNS): Guidelines on neurostimulation therapy for neuropathic pain (2007)[33]
The EFNS concluded that there was level B evidence for the effectiveness of SCS in FBSS and CRPS type I. Level B evidence indicates that SCS is probably effective. They also found positive evidence for SCS in the treatment of CRPS type II, peripheral nerve injury, diabetic neuropathy, post-herpetic neuralgia, brachial plexus lesion, stump pain, phantom lib pain, and partial spinal cord injury, but require confirmatory comparative trials for the unreserved recommendation of SCS use in these conditions[33].

Reflex Sympathetic Dystrophy Syndrome Association (RSDSA): Complex regional pain syndrome: treatment guidelines (2006)[34]
The RSDSA recommends that CRPS patients who are not progressing in the functional restoration/interdisciplinary algorithm to proceed in a stepwise progression from minimally invasive therapies (sympathetic nerve blocks, intravenous regional nerve blocks, and somatic nerve blocks) to more invasive therapies (neurostimulation, epidural and plexus catheter block(s), and intrathecal drug infusion), and finally to surgical and experiemental therapies (sympathectomy and motor cortex stimulation) in order to facilitate the patient's functional improvement and pain control[34].

Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic non-malignant pain syndrome patients (2005)[35]
Despite the growing number of studies and systematic reviews regarding the efficacy of SCS, the current guidelines do not recommend their use in chronic non-malignant pain syndrome patients given the continued absence of quality research[35].

2.6. Previous Systematic Reviews/Technology Assessments

Recent previously conducted systematic reviews and technology assessments identified one RCT evaluating SCS in patients with CRPS, and two RCTS appraising SCS in patients with FBSS. Most reviews concluded that there was some evidence to suggest that SCS was effective in improving pain among CRPS patients, and in improving pain and function among FBSS patients in the short term. All reviews noted that more multi-center, randomized-controlled trials are needed. Table 1 summarizes the previous assessments.

Table 1. Overview of previous technology assessments and systematic reviews of spinal cord stimulation for the treatment of neuropathic pain.

Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Health Technology Assessment, NIHR HTA Programme; School of Health and Related Research (ScHARR), University of Sheffield, UK[36] (used as basis for NICE policy) *Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation*	through 2007	*Medtronic* Itrel II or III System	CRPS • 1 RCT (%f/u NR); N = 54; compared SCS plus physical therapy (PT) with PT alone FBSS • 2 RCTs (%f/u NR); N = 160; one study compared SCS with CMM, and the other study compared SCS with reoperation	yes	• Adequate randomization and allocation of treatment	**Efficacy:** • CPRS - Suggests SCS was more effective than PT in reducing pain at six months and 2 years, but not at 5 years, and was more successful in terms of patients' GPE of treatment. • FBSS - Suggests SCS was more successful than CMM or reoperation in terms of pain relief. SCS resulted in more reduction in use of opiates than reoperation. SCS was more effective than CMM in improving functional ability. **Safety:** • SCS device-related complications include electrode migration, lead fracture, loss of paraesthesia, dural puncture, and infection (rates NR) **Economic:** • The results for the neuropathic pain model, over a 15-year time horizon, a device longevity of 4 years and a device cost of £7745, suggested that the cost effectiveness estimates for SCS in patients with FBSS who had inadequate responses to medical or surgical treatment were below £20,000 per quality adjusted life-year (QALY) gained. • In patients with CRPS who had had an inadequate response to medical treatment the ICER was £25,095 per QALY gained.

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Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Institute of Health Economics, Alberta (2008)[37] *Spinal cord stimulation for neuropathic pain*	through 2007	*Medtronic* Itrel II or III System	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone FBSS • 1 RCT (76% f/u); N = 100; compared SCS plus CMM • 1 SR (did not separate out CRPS and FBSS)	no	• No critical review, only author's conclusions given.	**Efficacy:** • CPRS – RCTs suggest level 2 evidence** that SCS decreases pain and improves functional status and quality of life in some people with neuropathic pain conditions. • FBSS - SCS improves pain relief, quality of life, functional capacity, and patient satisfaction, compared with CMM alone. **Safety**: • CPRS - reported infection and dural puncture, each at a rate of 1.2% • FBSS - device-related complications (32%), electrode migration (10%), infection (8%), loss of paresthesia (7%), adverse drug event (4%). **Economic**: NR
Ontario (MAS) (2005)[38] *Spinal cord stimulation for neuropathic pain*	through 2004	NR	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone • 3 prospective studies (% f/u NR); N = NR FBSS • 1 RCT (52% f/u); N = 51; compared SCS with reoperation	yes	CRPS • RCT graded 3/5 on the Jadad methodological quality score†† FBSS • RCT graded 4/5 on the Jaded methodological quality score	**Efficacy:** • CPRS - One RCT with level 2 evidence suggests that SCS decreases pain and improves functional status and quality of life in some people with neuropathic pain conditions. • FBSS - SCS was significantly better than reoperation for 90% of patients at three-year follow-up. **Safety**: • CPRS - Infection (1.4% to 11%); paralysis associated with infection at the tip of the lead (n =1); aseptic meningitis (n = 4); lead migration (rate NR). • FBSS - NR **Economic**: NR

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Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
The Cochrane Collaboration (2004)[39] *Spinal cord stimulation for chronic pain (Review)*	through 2003	*Medtronic* Itrel II or III System	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone FBSS • 1 RCT (52% f/u); N = 81; compared SCS with reoperation	yes	• Adequate randomization and allocation of treatment	**Efficacy**: • CPRS - Suggests SCS was more effective than PT in reducing pain, but not improving function, in patients with CRPS Type I. • FBSS - RCT provides limited evidence that SCS reduces the need for reoperation, however, the number of patients was small and the difference was not statistically significant. **Safety**: • CPRS - Of the 36 patients that received SCS, six and four experienced complications at six and 12 months post-implantation respectively. Long-term (i.e. 12 months) complications reported were infection (n = 1), subcutaneous dissections of the placement of the generators (n = 2), and defective lead (n = 1). • FBSS - NR **Economic**: NR
ASERNIP Report (2003)[40] *Spinal cord stimulation (neurostimulation): An accelerated systematic review*	through 2002	NR	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone FBSS • 1 RCT (52% f/u); N = 51; compared SCS with reoperation	yes	• Only included RCTs	**Efficacy:** • CRPS - Pain at six months was significantly reduced in the SCS plus PT group. Functional status and overall quality of life did not show any significant differences between groups. • FBSS - SCS was significantly better than reoperation for 90% of patients at three-year follow-up. **Safety**: • CRPS - SCS patients had a 38% complication rate in the 12 months post implantation, complications included dural puncture (n = 2); infection (n = 1); corrective lead positioning (n = 6). • FBSS - NR **Economic**: NR

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Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
WCB Evidence Based Practice Group (2003)[41] *Spinal cord stimulation use in patients with complex regional pain syndrome*	through 2002	NR	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone • 13 observational studies (% f/u NR); N = NR FBSS - NR	yes	CRPS • Focus on workers that had SCS implantation. FBSS - NR	**Efficacy:** • CRPS - Most workers who had SCS implanted, do not improve function significantly. Study concluded there was insufficient evidence that SCS is effective in treating CRPS. • FBSS - NR **Safety**: • CRPS - The complication rate varied between 20 to 75% of the evaluated studies (rates NR) • FBSS- NR **Economic**: NR
Frey (2009)[42] *Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review*	through 12/2008	NR	CRPS - NR FBSS • 2 RCTs (100% f/u); N = 150; one study compared SCS with CMM, and the other with reoperation. • 9 observational studies (% f/u NR); N = 861; patients received SCS, main outcome was graded pain relief.	yes	CRPS - NR FBSS • Reviewers concluded SCS evidence to be level II-1 or II-2 for clinical use on a long-term basis***	**Efficacy:** • CRPS - NR • FBSS - RCT results suggest SCS improved leg and back pain relief, quality of life, and functional capacity, as well as greater treatment satisfaction, compared with CMM or reoperation. Eight of nine (88%) of observational studies reported positive pain relief at >12 months. **Safety**: NR **Economic**: • CRPS - NR • FBSS - SCS is more effective and less costly in the long-term, but there is an initial high cost associated with the device implantation and maintenance.

Table 1. Overview of previous technology assessments and systematic reviews of spinal cord stimulation for the treatment of neuropathic pain.

Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Bala (2008)[43] *Systematic review of the (cost-) effectiveness of spinal cord stimulation for people with failed back surgery syndrome*	through 01/2008	*Medtronic* Itrel II or III System	CRPS - NR FBSS • 2 RCTs (100% f/u); N = 150; one study compared SCS with CMM, and the other study compared SCS with reoperation. • 1 retrospective cohort (% f/u NR); N = 104 • 13 case series (% f/u NR); N = 1,887	yes	CRPS - NR FBSS • 3 studies met inclusion criteria for economic analysis	**Efficacy:** • CRPS - NR • FBSS - There is some evidence that SCS is effective in the treatment of FBSS in terms of pain reduction. **Safety**: NR **Economic**: • CRPS - NR • FBSS - Three studies included in the economic evaluations concluded that SCS is both more effective and less costly in the long term. However, high costs associated with device implantation and maintenance suggests an incremental cost-effectiveness ratio that might put the ratio above commonly accepted levels of willingness to pay.
Taylor and Van Buyten (2006)[44] *Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors*	through 01/2002	*Medtronic* Itrel II or III System	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone • 25 case series (% f/u NR); N = 500 FBSS - NR	yes	CRPS • RCT scored grade A evidence, case series was grade D‡‡. FBSS - NR	**Efficacy:** • CRPS - RCT suggests SCS, combined with PT, is effective for the treatment of patients with CRPS type I. Case series focused on CRPS type II, and indicated on average, 67% of patients experience >50% pain relief with SCS. • FBSS- NR **Safety**: • CRPS - SCS device-related complications include electrode issues (20%); infections (4%); generator issues (2%); or extension cable issues (1%). • FBSS- NR **Economic**: • CRPS - Analysis by authors (RCT) report that although the costs for SCS plus PT exceed those of PT alone at 12 months, this difference was reversed over a lifetime analysis. • FBSS- NR

Table 1. Overview of previous technology assessments and systematic reviews of spinal cord stimulation for the treatment of neuropathic pain.

Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Taylor (2006)[45] *Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis*	through 01/2002	*Medtronic* Itrel II or III System	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone • 25 case series (% f/u NR); N = 500 FBSS • 1 RCT (52% f/u); N = 51; compared SCS with reoperation • 72 case studies (% f/u NR); N = NR	yes	CRPS • RCT scored grade A evidence, case series was grade D†† FBSS • Analysis reported grade B evidence for SCS	**Efficacy:** • CRPS - Concluded there is good evidence for the use of SCS in patients with refractory neuropathic back and leg pain or CRPS type I. • FBSS - At six-month follow-up, fewer patients in the SCS group opted for crossover to reoperation, and more patients receiving SCS achieved 50% or more pain relief, and required substantially less opiate analgesics than patients who underwent surgery. **Safety**: • CRPS - Data from eight studies indicated that overall 33% of CRPS patients experienced one or more problems with SCS. • FBSS - NR **Economic**: • CRPS - Analysis by authors (RCT) report that although the costs for SCS plus PT exceed those of PT alone at 12 months, this difference was reversed over a lifetime analysis. • FBSS - None specific for FBSS, but reported that over time SCS is cost saving to the system compared with conventional pain therapy or operation

Table 1. Overview of previous technology assessments and systematic reviews of spinal cord stimulation for the treatment of neuropathic pain.

Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Taylor (2005)[46] *Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: A systematic review and analysis of prognostic factors.*	through 01/02	NR	CRPS – NR FBSS • 1 RCT (52% f/u); N = 51; compared SCS with reoperation • 72 case studies (% f/u NR); N = NR	yes	CRPS – NR FBSS • Updated review from Taylor RS (1995); identified one RCT.	**Efficacy:** • CRPS – NR • FBSS - At six-month follow-up, fewer patients in the SCS group opted for crossover to reoperation, and more patients receiving SCS achieved 50% or more pain relief, and required substantially less opiate analgesics than patients who underwent surgery. Most case series reported pain relief using the threshold cutoff of 50% or more. **Safety**: • CRPS – NR • FBSS - Long-term complications reported included one infection, two IPG pocket-related complications, and one defective lead. **Economic**: NR

Table 1. Overview of previous technology assessments and systematic reviews of spinal cord stimulation for the treatment of neuropathic pain.

Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Cameron (2004)[47] *Safety and Efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review*	01/1981 through 2004	*Medtronic* Itrel II or III System	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone • 3 prospective uncontrolled (%f/u NR); N = 50 • 8 retrospective (%f/u NR); N = 210 FBSS • 1 RCT (52% f/u); N = 51; compared SCS with reoperation • 3 prospective uncontrolled (%f/u NR); N = 96 • 5 retrospective (%f/u NR); N = 228	no	• No critical review, only author's conclusions given (for both CRPS and FBSS)	**Efficacy:** • CRPS - In the RCT, pain at six months was significantly reduced in the SCS plus PT group. Functional status and overall quality of life did not show any significant differences between groups. The other studies also reported a significant improvement in pain scores compared to baseline, and a decrease in narcotic intake. • FBSS - In the RCT, significantly more patients crossed over from the surgery group to the SCS group compared with those that crossed over from the SCS group to the surgery group. In the uncontrolled studies, authors report that pain scores were significantly reduced compared with baseline and that pain medication was reduced. **Safety**: • CRPS - Complications were categorized from all studies examined, and included lead migration, infection, epidural hemorrhage, seroma, hematoma, paralysis, CSF leakage, over- or under-stimulation, allergic reaction, skin erosion, lead breakage, hardware malfunction, loose connection, and battery failure. • FBSS - Complications were categorized from all studies examined, and included lead migration, infection, epidural hemorrhage, seroma, hematoma, paralysis, CSF leakage, over- or under-stimulation, allergic reaction, skin erosion, lead breakage, hardware malfunction, loose connection, and battery failure. **Economic**: NR

Table 1. Overview of previous technology assessments and systematic reviews of spinal cord stimulation for the treatment of neuropathic pain.

Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Turner (2004)[48] *Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications.*	through 2003	*Medtronic* Itrel II or III System	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone • 1 case series (%f/u NR); N = 24 FBSS • 3 case series (% f/u NR); N = 120	yes	• Updated review (both CRPS and FBSS)	**Efficacy:** • CRPS - In the RCT, from baseline to one year, pain intensity decreased from an average of 7.1 to 4.4 in the group randomized to PT plus SCS, and increased from 6.7 to 7.1 in the group randomized to PT only ($P < 0.001$). • FBSS - Because the groups were not comparable at baseline, no conclusions can be drawn regarding the relative benefits of SCS versus medical therapy in improving patient functioning. **Safety**: • CRPS - In the RCT, 38% of patients reported complications (not described). • FBSS - Two of the three studies report complication rates of 33 and 60% (complications were not described). **Economic**: NR
Grabow (2003)[49] *Spinal cord stimulation for complex regional pain syndrome: an evidence based medicine review of the literature*	through 2002	NR	CRPS • 1 RCT (100% f/u); N = 54; compared SCS plus physical therapy (PT) with PT alone • 14 observational studies (% f/u NR); N = 340 FBSS - NR	yes	CRPS • Primary objective was to examine the efficacy of SCS. FBSS - NR	**Efficacy:** • CRPS - Authors concluded, based on the available evidence, that SCS was effective therapy for patients with CRPS who did not respond to more conservative medical management. • FBSS- NR **Safety**: • CRPS - The rate of complication due to technical problems ranged from 8.3% to 42.8%. The rate of reoperation ranged from 11.1% to 50%. • FBSS- NR **Economic**: NR

Table 1. Overview of previous technology assessments and systematic reviews of spinal cord stimulation for the treatment of neuropathic pain.

Assessment (year)	Lit search dates	Prosthesis evaluated	Evidence base available*†	Critical Appraisal ‡	Comments	Primary Conclusions
Turner (1995)[50] *Spinal cord stimulation for chronic low back pain: A systematic literature synthesis*	through 06/1994	*Medtronic* (device not specified)	CRPS – NR FBSS • 39 case series (% f/u NR); N = NR	no	CRPS – NR FBSS • Older review, no RCTs available	**Efficacy:** • CRPS – NR • FBSS - Because so few studies assessed patients systematically at yearly intervals after implantation, authors could not conclude any efficacy of SCS. **Safety**: • CRPS – NR • FBSS - Majority of complications were electromechanical (occurring in 20-75% of patients across studies, average 42%) **Economic**: NR

ASERNIP: Australian Safety & Efficacy Register of New Interventional Procedures
CMM: conventional medical management
CRPS: complex regional pain syndrome
FBSS: failed back surgery syndrome
f/u: follow-up
NIHR: National Institute for Health Research
NR: not reported
PT: physical therapy
SCS: spinal cord stimulation
SR: systematic review
WCB: Workers' Compensation Board (of British Columbia)

* Percent follow-ups were not given for all RCTs or case series
† N reflects numbers before loss to follow-up
‡ Critical appraisal refers to formal evaluation of individual study quality using criteria such as the Jadad or GRADE methods of scoring and the determination of overall strength of evidence.
** Strong evidence from at least one properly designed RCT of appropriate size.
†† Relevant RCTs were assessed using the instrument to measure the likelihood of bias in pain research reports developed by Jadad et al. (1996). One point is scored for each "yes" answer to the following questions: 1) Was the study described as randomized? 2) Was the study described as double blinded? 3) Was there a description of withdrawals and dropouts? Then, give one additional point if: For question 1, the method to generate the sequence of randomization was described and was appropriate. Or, deduct one point if: For question 1, the method to generate the sequence of randomization was described and it was inappropriate and/or for question 2, the study was described as double blinded but the method of blinding was inappropriate.
‡‡ Grades of recommendation: A = At least one high quality meta-analysis, or systematic review of RCT directly applicable to the target population, and demonstrating overall consistency of results; B = High quality systematic reviews of case-control or cohort studies; C = Well-conducted case-control or cohort studies with a low-risk of confounding, and demonstrating overall consistency of results; D = Evidence from non-analytic studies (case reports, case series).
*** The 5 levels of evidence were classified as Level I (the highest level of evidence), II, or III (the lowest level of evidence) with three subcategories in Level II based on the quality of evidence developed by the U.S. Preventive Services Task Force (USPSTF).

2.7. Medicare and Representative Private Insurer Coverage Policies

Coverage policies are consistent for spinal cord stimulation (SCS) for the Centers for Medicare and Medicaid Services and selected bell-weather payers. The payers will provide coverage for SCS, as long as implantation of the device is used as a late or last resort (after all other treatment modalities have failed, or SCS is deemed appropriate) and certain patient conditions are met. One exception to these coverage policies was found from the Washington State Department of Labor and Industries, who will not provide SCS coverage for a workers' compensation claim. Table 2 provides an overview of policy decisions.

National policy decisions:

- Medicare National Coverage Decision (1995)

The Centers for Medicare and Medicaid Services (CMS) will cover the use of SCS for the relief of chronic intractable pain when **all** of the following conditions have been met:

- SCS implantation is only used as a late or last resort for patients with chronic intractable pain;
- Patients have undergone careful physical and psychological screening by a team of physicians;
- There has been a previous demonstration of pain relief with temporarily implanted electrodes;
- Everything needed for the proper treatment and follow-up of the patient is available (ie., facilities, equipment, professional and support personnel, etc.); and
- SCS implantation employs percutaneous insertion of electrodes into the epidural space.

Local policy decisions:

- CMS local coverage decisions for Idaho (Pinnacle Business Solutions), Colorado (Trailblazer Health Enterprises), New Mexico (Trailblazer), Oklahoma (Trailblazer), Texas (Trailblazer), Virginia (Trailblazer), Arkansas (Pinnacle), and Louisiana (Linnacle) were identified and have no additions or changes to the CMS NCD as outlined above.

- Washington State Department of Labor and Industries (2009)
  Spinal cord stimulation (SCS) is a non-covered procedure for workers' compensation claims (both State Fund and Self-Insured) and for crime victims' claims based on the following:
  - Little evidence supporting superiority of SCS over alternative treatments;
  - Small advantage of SCS in improving leg pain and function at six months;
  - No advantage of SCS in improving leg pain, function, or any other measure at 12 or 24 months; and
  - Adverse events with both trial and permanent SCS including infections and persistent pain in the region of implanted components.

- BCBS Regence Group (Idaho, Oregon, Utah, and much of the state of Washington) (2009)
  Spinal cord stimulation may be considered medically necessary for the treatment of severe and chronic pain of the trunk or limbs (other than critical limb ischemia) that is refractory to other pain therapies, provided **all** the following conditions have been met:
  - The treatment is only used as a last resort; other treatment modalities (pharmacological, surgical, psychological, or physical) have been tried or failed or are judged to be unsuitable or contraindicated;
  - Pain is neuropathic in nature; i.e., resulting from actual damage to the peripheral nerves. Common indications include (but are not limited to): failed back syndrome, complex regional pain syndrome, arachnoiditis, radiculopathies, phantom limb/stump pain, and peripheral neuropathy;
  - No serious untreated drug habituation exists;
  - Patient was carefully screened, evaluated and diagnosed by a multidisciplinary pain management team prior to application of these therapies; and
  - Pain relief from a temporarily implanted electrode has been demonstrated prior to permanent implantation.

- BCBS (Florida)
  Permanent implanted spinal cord stimulator meets the definition of medical necessity for the treatment of severe and chronic, intractable neuropathic pain of the trunk or limbs when **all** of the following criteria are met.
  - The treatment is used as a last resort;
  - Other treatment modalities (pharmacological, surgical, physical or psychological therapies) have been tried and failed **or** the treatment modalities are judged to be unsuitable or contraindicated;
  - Demonstration of pain relief with a temporarily implanted electrode precedes permanent implantation.
  - Careful screening and diagnosis by a multidisciplinary team prior to implantation (such screening must include psychological, as well as physical evaluation); and
  - All the facilities, equipment, and professional and support personnel required for the proper diagnosis, treatment training, and follow-up of the patient are available.

Table 2. Overview of payer technology assessments and policies for spinal cord stimulation

Payer (year)	Lit search dates	Evidence base available*	Policy	Rationale/comments
National policies				
Centers for Medicare and Medicaid Services: NCD for Electrial Nerve Stimulators (160.7) (1995)	NR	NR	(CMS) will cover the use of electrical nerve stimulators under the prosthetic device benefit for implanted central nerve stimulators subject to **all** the following conditions: o Use is for dorsal column (spinal cord) neurostimulation; o Implantation of the device is used only as a late or last resort for patients with chronic intractable pain; o Patients have undergone careful physical and psychological screening by a team of physicians; o All facilities, equipment, and personnel required for proper diagnosis, treatment, and follow-up must be available; and o Demonstration of pain relief with a temporarily implanted electrode precedes permanent implantation.	a. No rationale for policy stated.
Local policies				
Washington State Department of Labor and Industries (Bulletin 09-04) (2009)	NR	• 1 SCS report conducted by University of Washington and sponsored by Labor & Industries (L & I)	Spinal cord stimulation is a non-covered procedure for workers' compensation claims (both State Fund and Self-Insured) and for crime victims' claims.	▪ Decision to not change the current policy was based solely on L&I-sponsored SCS study, final report submitted in 2008.
BCBS Regence Group (ID, OR, UT, much of WA) (2009)	through 2008	• 3 RCTs • 1 prospective multicenter study	Spinal cord stimulation may be considered medically necessary for the treatment of chronic pain of the trunk or limbs when **all** of the following criteria are met: o Treatment is only used as a last resort; other treatment modalities have been tried and failed or are judged to be unsuitable or contraindicated; o Pain is neuropathic in nature; i.e., resulting from actual damage to the peripheral nerves; o No serious untreated drug habituation exists;	• No rationale for policy stated • CPT codes if selection criteria is met: 63650

			o Patients have undergone careful physical and psychological screening; o Pain relief from a temporarily implanted electrode has been demonstrated prior to permanent implantation.	
BCBS (FL) Medical Policy (2010)	NR	• BCBS Medical Policy Reference Manual	Permanent implanted spinal cord stimulator meets the definition of medical necessity for the treatment of severe and chronic, intractable neuropathic pain of the trunk or limbs when **all** of the following criteria are met: o Treatment is only used as a last resort; o Other treatment modalities have been tried and failed or the treatment modalities are judged to be unsuitable or contraindicated; o Demonstration of pain relief with a temporarily implanted electrode precedes permanent implantation; o Patients have undergone careful physical and psychological screening; and o All the facilities, equipment, and personnel required for proper diagnosis, treatment, and follow-up of the patient are available.	▪ No rationale for policy given ▪ CPT codes if selection criteria is met: 63650

BCBS: Blue Cross Blue Shield
CMS: Centers for Medicare and Medicaid Services
L & I: labor and industries
NCD: National Coverage Decision
NR: not reported
RCT: randomized controlled trial
SCS: spinal cord stimulation
*Medicare and BCBS do not report the current evidence available.

3. The Evidence

3.1. Methods of the Systematic Literature Review

The primary aim of this assessment was to systematically review, critically appraise and analyze research evidence evaluating the efficacy, effectiveness, safety, and predictive factors for using spinal cord stimulators for the treatment of chronic neuropathic pain.

3.1.1. Inclusion/exclusion

Inclusion and exclusion criteria are summarized in Table 3.

- *Population.* Studies of adults who underwent permanent implantation of spinal cord stimulation for the treatment of chronic neuropathic pain due to conditions including (but not limited to) failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), phantom limb or stump pain, central pain such as post-stroke pain, diabetic neuropathy, and post-herpetic neuralgia. Diagnosis of neuropathic pain in at least 75% of patients was required for study inclusion.
- *Intervention.* Included studies that evaluated permanently-implanted spinal cord stimulation devices. Studies with the following types of interventions were excluded: studies reporting only on temporarily placed spinal cord stimulation devices; transcutaneous electrical nerve stimulation; and neurostimulation involving other parts of the nervous system (such as deep brain or peripheral nerves).
- *Comparator.* Included studies that compared spinal cord stimulation to medical and/or surgical treatment that does not included spinal cord stimulation, including but not limited to: conventional medical management, reoperation, physical therapy.
- *Outcomes.* Eligible studies reported on at least one of the following outcomes: pain, health-related quality of life, physical and functional abilities (not including measurements of range of motion, gait, strength, etc.), anxiety and depression, medication use, and complications (including but not limited to procedural complications, technical failures, device revision, infection). Studies reporting on non-clinical outcomes were excluded.
- *Study design.* Eligible studies compared spinal cord stimulation with alternative medical and/or surgical treatment utilizing a randomized or cohort study design. In order to provide additional context for key question 2, registry studies as well as studies with historical/nonconcurrent controls and/or summaries of case series with ≥ 5 years follow-up and >10 patients were included. For key question 3, only studies with LoE grades of I or II were included. Formal cost-effectiveness economic analyses published in peer-reviewed journals were eligible for inclusion to help answer key question 4.

Table 3. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Participants	Adults with: ◆ Neuropathic pain (including, but not limited to: failed back surgery syndrome, complex regional pain syndrome, phantom limb or stump pain, central pain such as post-stroke pain, diabetic neuropathy and post-herpetic neuralgia)	◆ Children ◆ Patients with prior use of SCS ◆ Patients who are pregnant
Intervention	◆ Spinal cord stimulation (permanently-implanted pulse generator systems and radiofrequency receiver systems)	◆ Temporarily-implanted spinal cord stimulation ◆ Neurostimulation that involved stimulation of other parts of the nervous system (e.g. peripheral nerves, deep brain). ◆ Transcutaneous electrical nerve stimulation
Comparators	◆ Medical and/or surgical treatment (appropriate to condition) that does not include SCS	
Outcomes	◆ Pain ◆ Patient satisfaction ◆ Global perceived effect (GPE) ◆ Health-related quality of life (HR-QoL) ◆ Function ◆ Anxiety and depression ◆ Medication use ◆ Complications and adverse effects (e.g. procedural complications and technical failures)	◆ Non-clinical outcomes
Study Design	◆ Comparative clinical studies (e.g. RCTs, cohort studies with concurrent controls) will be considered for questions 1-3 (question 3 is limited to studies with LoE of I or II) ◆ Case series with at least 5 years follow-up for question 2 ◆ Formal cost-effectiveness analyses will be sought for question 4	◆ Case reports ◆ Case series for questions 1 or 3 other than for context ◆ Case series with < 5 years follow-up for question 2 ◆ Studies with LoE III or IV for question 3 ◆ Non-clinical studies ◆ Studies with N < 10 patients total OR per group ◆ Studies in which < 75% of patients have chronic neuropathic pain
Publication	◆ Studies published in English in peer reviewed journals, published HTAs or publicly available FDA reports ◆ Full formal cost-effectiveness economic analyses published in English in an HTA, or in a peer-reviewed journal published after those represented in previous HTAs.	◆ Abstracts, editorials, letters, books ◆ Studies without abstracts available online (by searching Pubmed, google, and the journal's website if available) ◆ Duplicate publications of the same study which do not report on different outcomes

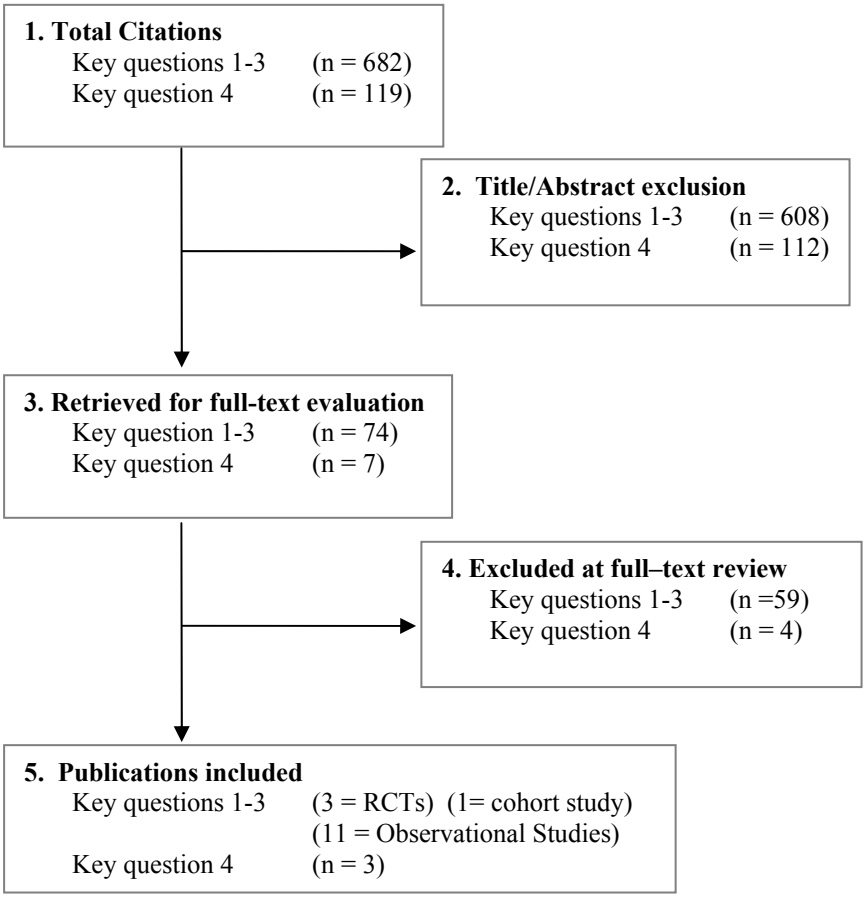
		◆ Single reports from multicenter trials ◆ Studies reporting on the technical aspects spinal cord stimulation ◆ White papers ◆ Narrative reviews ◆ Articles identified as preliminary reports when results are published in later versions ◆ Other types of economic evaluations (ie., costing studies, cost-minimzation analyses, cost-utility analyses, cost-benefit analyses)

3.1.2. Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Electronic databases searched included PubMed, EMBASE, CINAHL, ClinicalTrials.gov, CRISP, HSTAT, *The Cochrane Library*, EconLIT, PsychINFO, AHRQ, and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports. The databases were searched from inception through February, 2010. Reference lists of all eligible studies were also searched. The search strategies used for PubMed and EMBASE, are shown in Appendix B. Figure 1 shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed in Appendix C.

Figure 1. Flow chart showing results of literature search



3.1.3. Data extraction

Reviewers extracted the following data from the included clinical studies: study population characteristics, study type, study period, patient demographics and preoperative diagnoses, study interventions, follow-up time, study outcomes (pain, patient satisfaction, global perceived effect, health-related quality of life, anxiety and depression, function, medication usage, and "success"), adverse events (reoperation, device-related complications, and other complications or side effects). An attempt was made to reconcile conflicting information among multiple reports presenting the same data. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted.

3.1.4. Study quality assessment: Level of evidence (LoE) evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine[51], precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE)

Working Group[52], and recommendations made by the Agency for Healthcare Research and Quality (AHRQ)[53].

Details of the Level of Evidence (LoE) methodology are found in Appendix E. Each clinical/human study chosen for inclusion was given a LoE rating based on the quality criteria listed in Appendix D. Standardized abstraction guidelines were used to determine the LoE for each study included in this assessment.

3.2. Data Analysis

3.2.1. Quality of studies retained

We initially found 682 citations using the search strategy in Appendix B. For Key Question 1 we identified 11 reports that compared SCS with conventional medical management or reoperation. From among these, three RCTs and one prospective cohort study met our inclusion criteria. Two RCTs were graded as LoE I; one RCT and one cohort study received the LoE grade of II. Critical appraisals of the RCTs and cohort study are included in the results section. Due to the nature of the SCS intervention, one of the limitations of all of the included studies is that blinding is impossible.

For Key Question 2 on safety, we included in addition to the studies cited in the preceding paragraph, six case series. All the case series received the LoE grade of IV.

To address outcomes following total HR in special populations (Key Question 3), we included four prospective and two retrospective cohort studies. One of the cohort studies received the LoE grade of I and the remaining five received the LoE grade of II.

3.2.2. Outcome measures

The studies included in this assessment used a variety of measures to evaluate treatment outcomes, which are outlined in Table 4. The 10-cm visual analogue scale (VAS) was the most commonly used tool for assessing pain intensity and pain relief. Visual pain scales are used in studies of pain treatment as a tool for quantifying pain relief or improvement between pre- and post-treatment measurements; the changes in pain intensity are compared between treatment groups.

Table 4. Outcome measures

Outcome measure	Clinician or patient reported	Instrument type	Components	Score range	Interpretation
Beck Depression Inventory[54]	Patient	Generic	21 items that assess the existence and severity of depression	0–63	Higher score = greater severity of depression
Derogatis Affects Balance Scale (DABS)[55]	Patient	Generic	40 single-word adjectives that describe positive and negative moods, in the following dimensions: Positive: Affection Contentment Joy Vigor Negative: Anxiety Depression Guilt Hostility	Percentile based on standardized norms	
EQ-5D (European Quality of Life)[56]	Patient	Generic	Mobility (1–3) Self-care (1–3) Usual activity (1–3) Pain (1–3) Anxiety/depression (1–3)	0–1*	Optimal health: 1 Death: 0
Global Perceived Effect[25]	Patient	Generic	Effect	1–7	1: worst ever 2: much worse 3: worse 4: not improved and not worse 5: improved 6: much improved 7: best ever
McGill Pain Questionnaire[57]	Clinician	Generic	Pain rating index (PRI) (20 items total spanning four categories: sensory, affective, evaluative, and miscellaneous) Present pain intensity (PPI) Pain location (no score) Pain change over time (no score)	PRI: 0–78 PPI: 1–5	Higher scores = greater pain disability
Minnesota Multiphasic Personality Inventory-2 (MMPI)[58]	Patient	Generic	Hypochondriasis Depression Hysteria Psychopathic deviate Masculinity-femininity Paranoia Psychasthenia Schizophrenia Hypomania Social introversion		567 items total, each item is a “true” or “false” statement Interpretation is complex and should only be performed by psychologists.
Nottingham Health Profile[59]	Patient	Generic	Physical mobility Pain Sleep Emotional reactions Social isolation Energy level	0–100	Higher scores = lower function
ODI (Oswestry Disability Index, or Oswestry Low Back Pain Disability	Patient	Back	Pain intensity Personal care Lifting Walking	0–100†	Higher scores = greater disability

Questionnaire) (version 2.0)[60]			Sitting Standing Sleeping Sex life Social life Travelling		
Pain Catastrophizing Score (PCS)[61]	Patient	Generic	13 items that identify a patient's catastrophic thoughts or feelings	0–52	Higher score = more catastrophizing thoughts or feelings
Patients Global Impression of Change (PGIC)[62]	Patient	Generic	Effect	1–7	1: very much worse 2: much worse 3: minimally worse 4: no change 5: improved 6: much improved 7: very much improved
Roland-Morris Disability Questionnaire (RDQ)[63]	Patient	Back	Pain intensity Self care Social life Walking Sitting Standing Sleeping Bending Stairs Appetite General activity Household chores	0–24	Higher scores = greater disability
Self-Rating Depression Scale[64] (SDS)	Patient	Generic	Symptomatically negative (10 questions) Symptomatically positive (10 questions)	Raw score: 20–80 SDS index: 0.25–1.0 (raw score/80)	Higher scores = greater level of depression
SF-36 (Short Form 36 health survey questionnaire)[65]	Patient	Generic	8 subscales (# items) Physical functioning (10) Role limitations due to physical health problems (4) Bodily pain (2) General health (5) Vitality (4) Social functioning (2) Role limitations due to emotional problems (3) Mental health (5)	0–100 for each subscale (total score not used)	Lower score = greater disability
Sickness Impact Profile[66, 67]	Patient	Generic	Sleep and rest Eating Work Home management Communication Physical dimension (ambulation, mobility, self care) Psychosocial dimension (social interaction, alertness, emotional behavior, recreation)	0–100% (sum of score as a percentage of max. possible score (136))	Higher scores = greater disability
Symptom Checklist-90 Revised[68]	Patient	Generic	Somatization Obsessive-compulsive Interpersonal sensitivity Depression Anxiety	0–360	Higher scores = greater degree of global psychological distress

			Hostility Phobic anxiety Paranoid ideation Psychoticism Global severity index Positive symptom distress index Positive symptom total		
VAS pain (Visual Analogue Scale)	Patient	Generic	Pain	0–10 cm	No pain: 0 Worst pain imaginable: 10

* EQ-5D: final score is a 5-digit descriptor that corresponds to the level of disability in each subcomponent and ranges from 11111–33333; each score is assigned a preferential weight (e.g., 21111 = 0.85) that is based on a large sample of a population to obtain a final utility score of -0.594 to 1. The utility scores reported in the PROCESS trial were based on a sample of the UK population.[69]

† ODI: Each of the ten subscales is scored on a scale of 0–5 points; the total score is then doubled for a final score ranging from 0–100 points.

3.2.3. Clinically meaningful improvement

Statistical significance is commonly used to determine whether one treatment yields clinically improved outcomes compared to another. However, it is not the only factor that should be used to determine whether an outcome is clinically meaningful, and a statistical significant difference between treatment groups does not necessarily mean that the difference is meaningful to the patient. In order to best understand the efficacy of a treatment, it is important to determine what change in the outcome measure is equivalent to a clinically meaningful improvement for the patient[70]. The definition of clinically meaningful improvement varies throughout the medical literature with the conditions and outcomes being assessed as well as with the interested clinicians.

In this technology assessment, the most common outcome measure used to evaluate the efficacy of SCS is ≥50% reduction in VAS pain intensity compared to baseline. However, there are inconsistencies throughout the literature on what amount of pain relief constitutes a clinically meaningful improvement. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group, which is composed of 40 individuals from universities, governmental agencies, the pharmaceutical industry, and a patient organization, recommends that a 10–20% reduction in chronic pain be considered a minimally important difference, while a ≤30% decrease be considered moderately important and a ≤50% decrease be considered a substantially important difference. However, they note that more studies need to be conducted in order to systematically determine the clinically important difference in a variety of outcome measures used to evaluate treatments in chronic pain patients[70]. Differences in other outcome measures reported here should be considered in the same vein.

4. Results

For key question 1, we identified a total of three RCTs and one prospective cohort study. One RCT included only patients with complex regional pain syndrome (CRPS-I); two RCTs included only patients with failed back surgery syndrome (FBSS). Heterogeneity between these studies prevented pooling of the data. Two RCTs were graded as LoE I; one RCT and one cohort study received the LoE grade of II (Appendix E). The prospective cohort study was conducted specifically on Washington state workers' compensation patients with FBSS; we did not identify cohort studies on any other populations that met our inclusion criteria. The demographics for the comparative studies are summarized in Table 5, below. For key question 2, we identified six additional case series, all with mid-term follow-up. For key question 3, we identified four prospective and two retrospective cohort studies; one study received an LoE of I, while the other five received an LoE grade of II (Appendix E).

Table 5. Demographic Table: Spinal Cord Stimulation Comparative Studies

Author (Year)	Study Type	Follow-up (% follow-up)	Patient Characteristics	Preop diagnosis	Treatment	Successful trial stimulation; permanent implant	Study Sponsor
Kemler 2000, 2004, 2008	RCT Maastricht University Hospital; Maastricht, Netherlands	6 months (100%) 24 month (94%) 60 month (81%)	N = 54 Mean age: 38 yrs Sex: 31% male	Chronic CRPS I	• SCS + PT (n = 36) • PT alone (n = 18)	24/36 (67%)	Study supported by a grant from the Dutch Health Insurance Council)
Kumar 2007 (PROCESS trial)	RCT 12 centers in Europe, Canada, Australia, and Israel	6 months (94%) 12 months†† (88%)	N = 100 Mean age: 50 yrs Sex: 51% male	FBSS with leg pain exceeding back pain	• SCS + CMM (n = 52) • CMM: (n = 48)	43/52 (83%)	Study managed and funded by Medtronic
North 2005	RCT Johns Hopkins University Hospital	2.9 ± 1.1 yrs (range:1.8–5.7) (75%)	N = 60 Mean age: 50 yrs Sex: 50% male	FBSS with leg pain exceeding or equal to back pain	• SCS (n = 30) • Reoperation (n = 30)	17/24 (71%)	Study funded by Medtronic; Johns Hopkins received profits from a sale of Stimsoft, Inc., which was developing pain stimulator technology, to Medtronic
Turner 2010	Prospective cohort study Providers for the WA state workers' comp program	24 months (87%)‡‡‡‡	N = 159 Mean age: 44 yrs Sex: 77% male All patients had an open workers' compensation claim with the state of Washington	FBSS with leg pain exceeding back pain	• SCS (n = 51) • Pain clinic (n = 39) • Usual care (n = 68)	27/51 (52%)	Study funded by Washington State Department of Labor and Industries, which administers the workers' comp provider for the enrolled patients

4.1. Key question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation for the treatment of neuropathic pain compared with other treatments for pain?

4.1.1. Efficacy

Complex regional pain syndrome (CRPS)

Kemler (2000, 2004, 2008)[25, 71, 72]

Critical appraisal and overview
Kemler et al.[25, 71, 72] conducted a randomized controlled trial (RCT) in which 54 patients with severe chronic pain caused by complex regional pain syndrome type I (CRPS-I) (referred to as reflex sympathetic dystrophy) received either spinal cord stimulation (SCS) (with physical therapy) (PT) or physical therapy alone. Data were collected at 6 (100% follow-up)[25], 24 (94% follow-up)[71], and 60 months (81% follow-up)[72]. Mean patient age was 38 years, and 69% of patients were female. CRPS affected the hand (61%) or foot (39%), and was caused by trauma (48%), surgery (44%), or developed spontaneously (7%). The mean duration of chronic pain was 38 months.

Patients were randomized in a 2:1 fashion to SCS + PT (n = 36) or PT alone (n = 18). Those randomized to SCS + PT underwent a trial stimulation using a temporary lead and an external stimulator for at least seven days, and the trial was considered successful if either of the following conditions were met: (1) VAS score for the last four days of trial stimulation was at least 50% lower than the baseline score, or (2) the global perceived effect (GPE) score was at least 6 ("much improved") out of 7. Trial stimulation was successful in 67% (24/36), these patients went on to receive permanent SCS implants. Thirty-three percent (12/36) did not have successful trial stimulation and were treated with PT alone. Physical therapy consisted of a standardized program of graded exercises geared at improving strength, mobility, and function and was required only for the first six months: at two years follow-up, 21/51 available patients (9 randomized to SCS + PT, 12 randomized to PT) were still undergoing physical therapy[71]; this information was not reported at five years follow-up[72]. Cross-over was permitted after six months: the cross-over rate in the PT group was 11% (2/18) and 22% (4/18) at two and five years, respectively. Aside from those that failed trial stimulation, no patients randomized to SCS crossed over. Exact numbers for patients receiving each treatment at six months, two years, and five years can be found in the table below (see also Supplemental Table 1).

Outcome measures included pain (VAS, McGill Pain Questionnaire), global perceived effect (GPE), and health-related quality of life (HR-QoL) (VAS, Nottingham Profile pain component, EQ-5D, Self-Rating Depression Scale); outcomes were primarily reported as change in score from baseline.

This study received a Level of Evidence (LoE) grade of I (Appendix E). One of the limits of the study is that only patients who had been unresponsive to six months of physical therapy

met the inclusion criteria, thus this RCT compares SCS to a treatment known to be ineffective. Randomization was performed using a computer-generated table of random numbers and stratified according to the location of the CRPS (ie., hand or foot); the authors stated that the treatment assignments were made by an uninvolved research assistant and concealed from the study investigators[25, 71]. Due to the nature of the treatment, blinding of patients and investigators was not possible. Data were analyzed according to the intention-to-treat principle; however, patients in the PT group who crossed over were excluded while those in the SCS+PT group who did not receive permanent implants due to unsuccessful trial stimulation were not excluded from the intention-to-treat analysis. Outcomes were also compared for patients who actually received permanent SCS implants to those randomized to undergo PT alone (excluding those that crossed over). This study was funded by the Dutch Health Insurance Council and was conducted in the Netherlands.

The following table provides patient numbers available for follow-up for each treatment and data collection point:

	SCS + PT (n = 36 randomized)		**PT alone (n = 18 randomized)**	
	Implant received	**No implant**	**PT**	**Crossed over**
Initial treatment	n = 24	n = 12	n = 18	-
Treatment at 6 months	n = 24	n = 12	n = 18	-
Treatment at 24 months	n = 24*	n = 11*	n = 16*	n = 2†
Treatment at 60 months	n = 22	n = 9	n = 13	n = 4† (total)

* Physical therapy was mandatory until 6 months and optional thereafter. At 24 months, 9/36 patients randomized to SCS+PT and 12 patients randomized to PT alone were still undergoing physical therapy. These data were not reported for the 60-month follow-up.
† Patients in the PT group that crossed over were excluded from the intention-to-treat analyses.

The following outcomes were evaluated:

Pain: VAS (Figure 2)

As depicted in Figure 2a, patients randomized to receive SCS + PT had significantly improved pain as measured by the VAS compared with those assigned to receive PT alone at 6 months ($P < .001$) and 24 months ($P = .001$)[25, 71]. This difference was no longer significant by 60 months ($P = .25$)[72]. The differences in mean VAS scores compared with baseline for the SCS+PT group were -2.4 cm (6 months), -2.1 cm (24 months), and -1.7 cm (60 months); for the PT group there were changes of 0.2 cm (6 months), 0 cm (24 months), and -1.0 cm (60 months).

For those patients who received a permanent SCS implant only, the differences in mean VAS scores from baseline were -3.6 cm (6 months), -3.0 cm (24 months), and -2.5 cm (60 months). These results were significantly improved compared with patients randomized to the PT group at 6 months ($P < .001$) and 24 months ($P < .001$) but not at 60 months ($P = .06$)[25, 71, 72].

There was no significant difference in the mean VAS scores between groups for those patients available at follow-up at 0, 36, 48, or 60 months[73]; p-values were not reported for this subset of patients for 12 and 24 months follow-up (Figure 2b). The estimated mean VAS scores for the subset of SCS + PT patients who received permanent SCS implants are included in Supplemental Table 3.

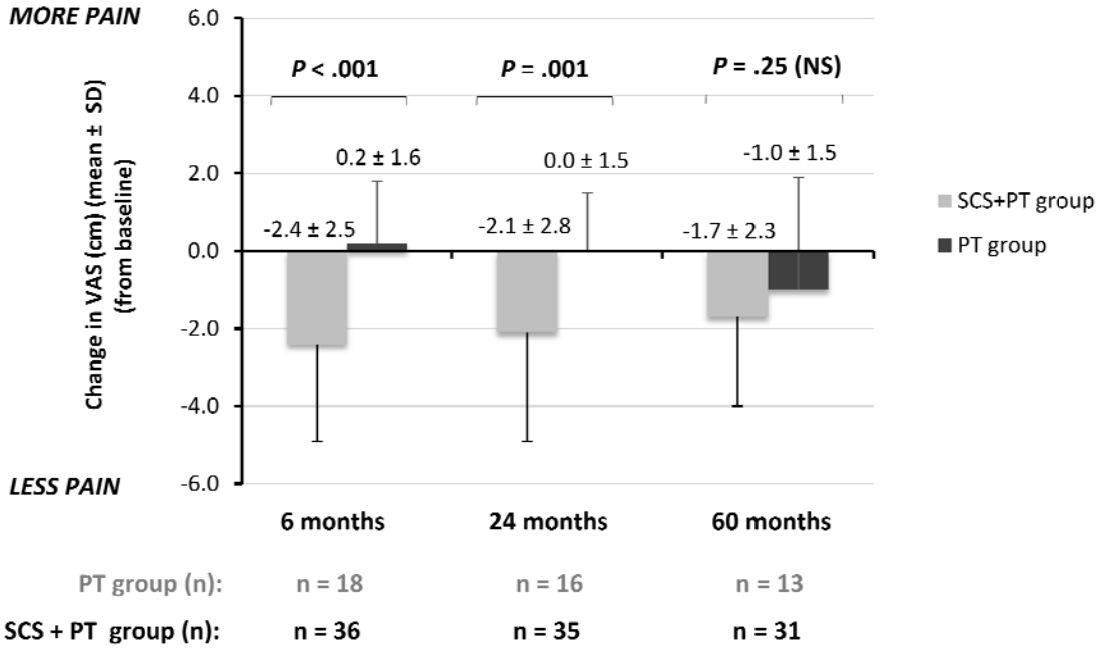
The authors commented that at 6 and 24 months, patients with an affected hand versus those with an affected foot had similar pain relief, however no other details or data were given[25, 71]. No information was given for the 60-month outcomes[72].

Pain: McGill Pain Questionnaire

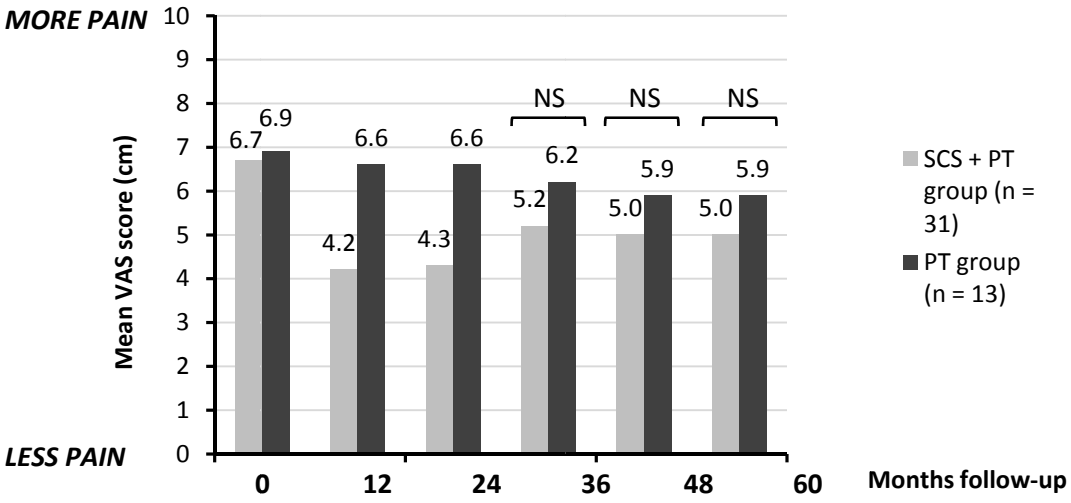
Patients who received permanent SCS implants had significantly better McGill Pain Questionnaire pain rating index scores than did those randomized to receive PT alone at 24 months (data not reported; $P = .02$)[71]. No data were reported for the 6- or 60- month follow-ups[25, 72].

Figure 2. Change in pain scores for CRPS-I patients treated with SCS + PT compared with PT alone: data from one randomized controlled trial.

a. Change in VAS scores (intention-to-treat analysis)[25, 71, 72]



b. Mean VAS scores of patients available at final follow-up[73]



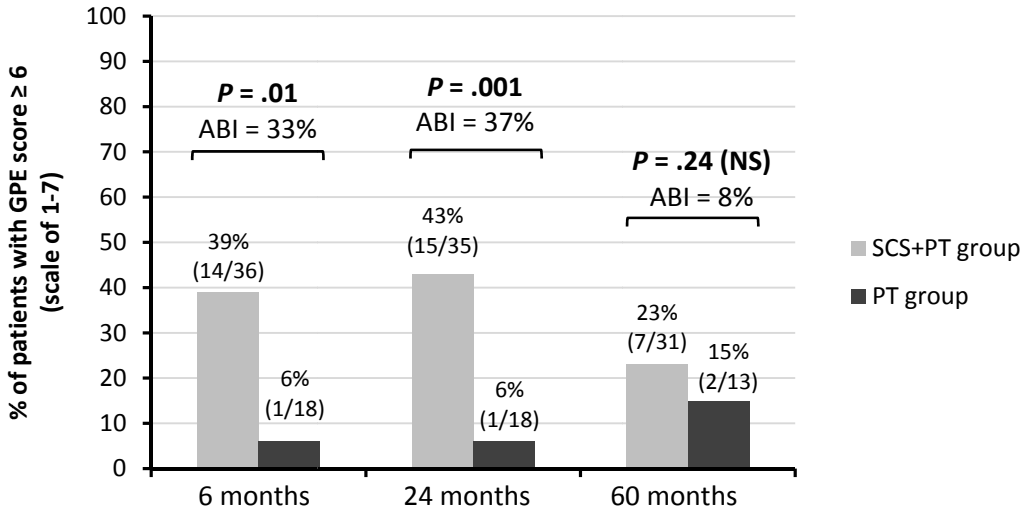
Global Perceived Effect (GPE) (Figure 3)

Significantly more patients randomized to SCS + PT had a GPE score indicating "much improved" or "best ever" (corresponding to a score of 6 or 7 on a scale of 1–7) than those assigned to receive PT alone at 6 months (39% versus 6%; absolute benefit increase, 33%; *P* = .01)[25] and 24 months (43% versus 6%; absolute benefit increase, 37%; *P* = .001)[71]. However, there was no difference at 60 months (23% versus 15%; absolute benefit increase, 8%; *P* = .24)[72] (Figure 3).

When comparing only those patients who received permanent SCS implants to patients in the PT group, there was a statistically significant difference in the percentage of patients with GPE scores of "much improved" or better in favor of SCS at all follow-ups: 6 months (58% versus 6%; absolute benefit increase, 52%; *P* < .001), 24 months (63% versus 6%; absolute benefit increase, 57%; *P* < .001), and 60 months (35% versus 15%; absolute benefit increase, 20%; *P* = .02).

The percent and number of patients with each GPE score at all follow-ups are detailed in Supplemental Table 3.

Figure 3. Percent of CRPS-I patients treated with SCS + PT compared with PT alone who reported "much improved": data from one randomized controlled trial[25, 71, 72].



Health-related quality of life (HR-QoL)

Kemler et al. reported HR-QoL using several different outcome measures:

Patients reported their perceived health-related quality of life using a VAS (range, 0 (death) to 100 (perfect health)); the mean percent change from baseline was similar in both groups at the 6-month and 24-month follow-ups: SCS + PT (6 ± 22%) versus PT alone (3 ± 18%) (*P* = .58) at 6 months[25]; SCS + PT (7 ± 20%) versus PT alone (12 ± 18%) (*P* = .41) at 24 months[71]. This outcome was not reported for 60 months follow-up[72]. Similar results were reported for patients randomized to SCS + PT who underwent permanent SCS implantation: 11 ± 23% (*P* = NR versus PT group) at 6 months and 12 ± 21% at 24 months (p-values were not reported)[25, 71].

At sixty months follow-up, no significant differences were found in three different outcome measures that assessed health-related quality of life (Nottingham Health Profile, EQ-5D, and Self-Rating Depression Scale) for the SCS + PT group compared with the PT group alone; similar results were found when comparing only the SCS + PT patients who received implants to those in the PT group[72]. Detailed scores can be found in Supplemental Table 3. Results of these outcome measures were not reported for earlier follow-ups[25, 71].

Failed back surgery syndrome (FBSS)

PROCESS Trial: Kumar (2007, 2008)[13, 74]; Manca 2008[69]

Critical appraisal and overview
The Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation (PROCESS trial) was an international RCT led by Kumar et al.[13] that compared SCS with conventional medical management (CMM). One hundred patients with failed back surgery syndrome (FBSS) and leg pain that exceeded back pain were enrolled in twelve centers in Europe, Canada, Australia, and Israel; details of the inclusion and exclusion criteria are outlined in Supplemental Table 2. Data were collected at 6 (94% follow-up)[13, 69], 12 (94% follow-up)[13], and 24 months (81% follow-up)[74]. However, due to the high rate of cross-over after six months, the intention-to-treat analysis was performed for the 6-month follow-up only. Mean patient age was 50.4 years, and 51% of patients were male. The mean duration of chronic pain was not reported, but was at minimum six months following the initial failed surgery[13].

One hundred FBSS patients were randomized to receive either SCS + CMM (n = 52) or CMM alone (n = 48). Trial SCS stimulation was conducted on all patients in the SCS + CMM group (the length of and devices used in the trial were not reported). Patients who met both of the following criteria were considered to have had a successful trial: (1) leg pain relief of at least 50%, and (2) a minimum paresthesia-pain overlap of 80%. A total of 48 patients received permanent SCS implants, including the 43 (83%) who had a successful trial as well as 5 others who failed trial stimulation but requested to continue with permanent SCS; the remaining 4 patients who did not have successful trial stimulation and were treated with CMM alone. CMM consisted of individualized therapy that was reviewed for each

patient at baseline and included a variety of oral medications as well as physical, psychological, and/or chiropractic treatments (see Supplemental Table 1 for details). Cross-over was permitted after six months: in the SCS + CMM group, 10% (5/50) of available patients had crossed over to CMM alone (four had insufficient pain relief and one had an "allergic reaction") by twelve months; it was not clear whether any additional SCS + CMM patients had crossed over by 24 months. The rate of cross-over in the CMM group was much higher: by 12 months, 73% (32/44) had requested to cross over to SCS (28/32 had successful trial stimulation and received permanent implants), by 24 months, 73% (30/41) of available patients had crossed over. More details for patient numbers at each follow-up are reported in the table below as well as in Supplemental Table 1.

The primary outcome measure was the percent of patients that achieved 50% or more leg pain relief (VAS) at 6 months. Secondary outcomes included back and leg pain (VAS), patient satisfaction (including return to work), health-related quality of life (HR-QoL) (SF-36 and EQ-5D), function (Oswestry Disability Index), and medication usage. Intention-to-treat analysis was used for 6-month data only; per-protocol analysis or "modified intention-to-treat analysis" was used for 12- and 24-month data due to the high amount of cross-over.

This study received a Level of Evidence (LoE) grade of I (Appendix E). The primary limit of the study is the high amount of cross-over after the six-month follow-up: because over 70% of patients randomized to CMM went on to receive SCS after six months, data from the 12- and 24-month follow-ups could not be analyzed using the intent-to-treat principle. Like the RCT done by Kemler et al.[25], another drawback is that patients included in the study had all been unresponsive to six months of conventional therapy, thus this RCT compares SCS to an ineffective treatment. Randomization was done by a biostatistician and utilized random computer-generated blocks; randomization was locked and was inaccessible prior to patient enrollment. Due to the nature of the treatment, blinding of patients and investigators was not possible. Outcomes were analyzed according to the intention-to-treat principle at the six month follow-up. Of note, the study was managed in part and funded by Medtronic, Inc., although additional independent researchers were involved in the oversight of the study and data analysis; the study was conducted in an international (non-US) setting.

The following table provides patient numbers available for follow-up for each treatment and data collection point:

	SCS + CMM (n = 52 randomized)		CMM alone (n = 48 randomized)	
	Implant received	**No implant (including cross-over)***	**CMM**	**Crossed over**
Initial treatment	n = 48	n = 4	n = 48	-
Treatment at 6 months	n = 50†		n = 44†	-
Treatment at 12 months	n = 47‡		n = 41‡,**	
Treatment at 24 months	n = 42	n = 4	n = 11**	n = 30

* Cross-over was permitted AFTER 6 months; the number of patients receiving each treatment was provided at each follow-up (but patients not receiving SCS were not separated out into those who had failed trial stimulation versus those who crossed over).

† At 6 months, some patients were lost due to withdrawn consent (SCS + CMM: n = 2; CMM: n = 4). For the SCS + CMM group, however, the authors did not report whether these two patients had received permanent implants.

‡ At 12 months, some patients were lost or had withdrawn consent (SCS + CMM: n = 5; CMM: n = 7 (total)). The authors did not report for either group whether these patients had received permanent implants, only that 47 patients were included in the 12-month analysis for the SCS group (by 12 months, 45 patients had received SCS only, and 5 patients had crossed to CMM) and that 41 patients were included for the CMM group (by 12 months, 16 patients had received CMM only, and 28 had crossed to SCS).

** At 12 and 24 months, respectively, 25% (4/16) and 27% (3/11) of the patients receiving CMM alone had requested to cross to SCS but failed trial stimulation.

The following outcomes were evaluated:

Leg pain relief ≥ 50% (primary outcome) (Figure 4a)

Intention-to-treat analysis (6 months): At six months follow-up, significantly more patients randomized to the SCS + CMM group had achieved at least 50% leg pain relief compared with those assigned to receive CMM alone (48% versus 9%, respectively; absolute benefit increase, 39%; $P < .001$) when analyzed using the intention-to-treat principle. The relative risk (RR) is 5.28 with a 95% confidence interval (CI) ranging from 1.99 to 14.04.

At 12- and 24- months follow-up, intention-to-treat analysis could not be performed due to the high rate of cross-over after 6 months[13, 74].

Sensitivity analysis (6 months): A sensitivity analysis was also performed, which excluded those patients in the SCS group who failed trial stimulation but requested permanent SCS implants (n = 5), and showed similar results (SCS: 51% versus CMM: 9%; absolute benefit increase, 42%; $P < .001$).

"Worst-case" analysis (6 & 24 months): Even in a "worst-case" analysis (patients withdrawn in the SCS group were considered failures and in the CMM were considered successes),

statistical significance remained at 6 months (SCS: 46% versus CMM: 17%; absolute benefit increase, 29%; $P = .002$)[13]. At the 24-month follow-up statistical significance was not reached (SCS: 33% versus CMM: 17%; $P = .07$; relative risk, 1.96 (95% CI, 0.93, 4.1)[74].

Per-protocol analysis (12 & 24 months): According to a per-protocol analysis, significantly more patients being treated with SCS + CMM at both 12- and 24- months had achieved at least 50% leg pain relief compared with those whose most recent treatment was CMM (12 months: 48% versus 18%, respectively; absolute benefit increase, 30%; $P = .03$; relative risk, 2.71 (95% CI, 0.94, 7.79))[13], (24 months: 47% versus 7%, respectively; absolute benefit increase, 40%; $P = .02$; relative risk, 7.08 (95% CI, 1.05, 47.80))[74].

Modified intention-to-treat analysis (12 & 24 months): Similar results were found using a *post hoc* modified intention-to-treat analysis, in which patients who crossed over were considered failures (12 months: 34% (SCS) versus 7% (CMM); absolute benefit increase, 27%; $P = .005$; relative risk, 4.65 (95%, 1.46, 14.84))[13], (24 months: 37% (SCS) versus 2% (CMM); absolute benefit increase, 35%; $P = .003$; relative risk, 15.15 (95% CI, 2.11, 108.91)[74].

Leg and back pain relief (secondary outcomes) (Figure 4)

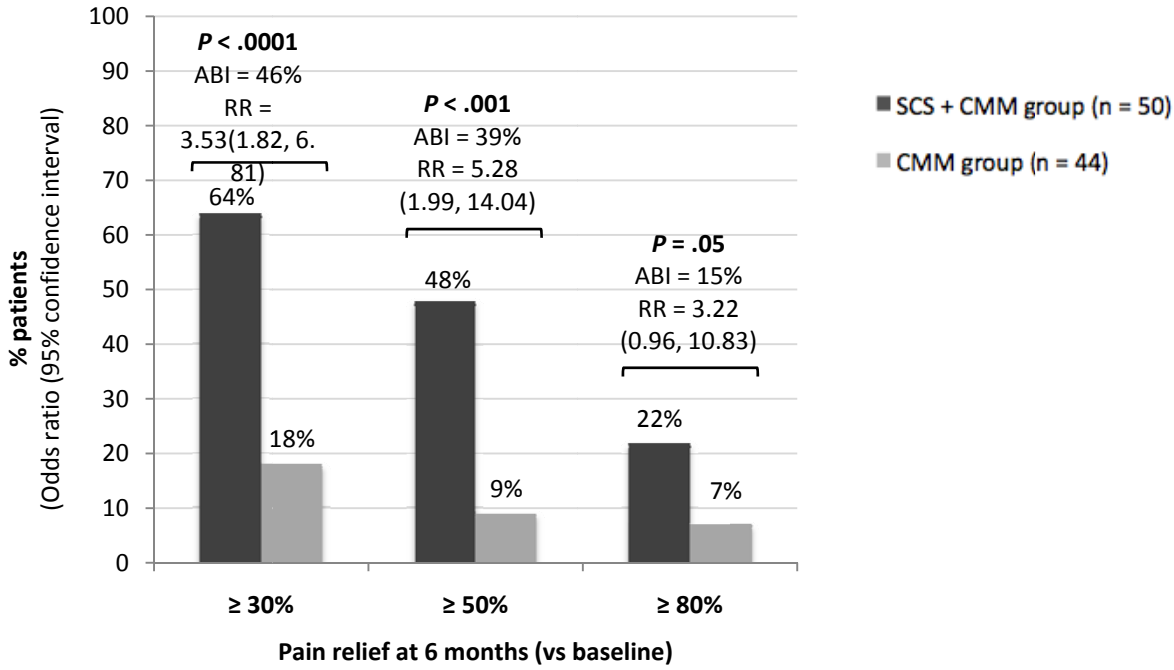
As shown in Figure 4a, significantly more patients in the SCS + CMM group achieved at least 30% leg pain relief at six months than those in the CMM group (64% versus 18%, respectively, $P < .0001$). These results corresponded to an absolute benefit increase of 46% and a relative risk of 3.53 (95% CI, 1.82, 6.81). Although more patients in the SCS + CMM group experienced at least 80% leg pain relief at the same follow-up compared with CMM patients, this result did not reach statistical significance (22% versus 7%, respectively; absolute benefit increase, 15%; $P = .05$; relative risk, 3.22 (95% CI, 0.96, 10.83)).

The mean VAS for leg pain at 6 months was significantly better for patients in the SCS + CMM group than for patients randomized to receive CMM alone (3.99 ± 2.63 versus 6.66 ± 2.40, adjusted $P < .0001$). The authors adjusted the p-value (but not the scores) for baseline values and covariates (including sex, age, time since original surgery, number of prior surgeries, and leg pain location). The leg pain VAS scores at six months were significantly lower for both groups of patients compared with baseline (SCS: 3.99 ± 2.63 versus 7.60 ± 1.30 (baseline), $P < .0001$ (unadjusted)) (CMM: 6.66 ± 2.40 versus 7.34 ± 14.0 (baseline), $P = .03$ (unadjusted)) (Figure 4b). While the improvements in the CMM group were more modest, they still achieved statistical significance.

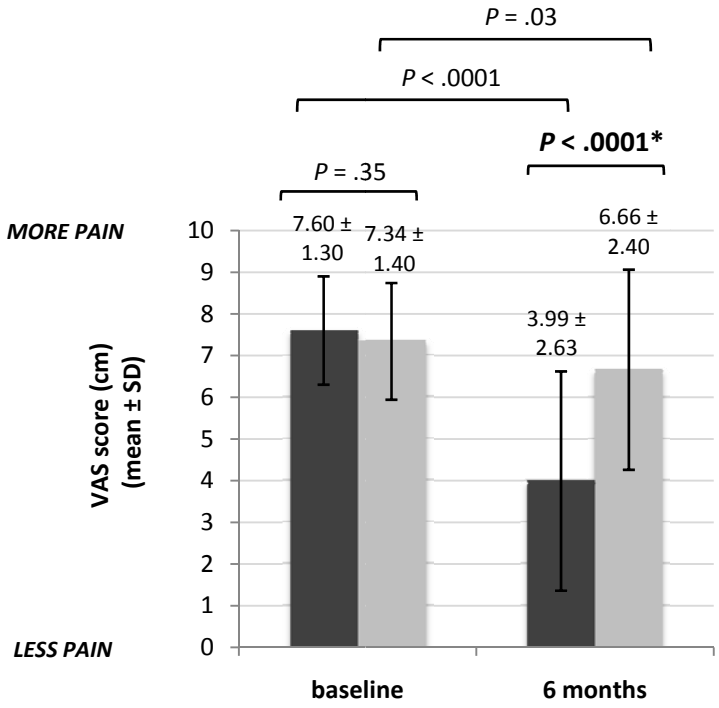
SCS patients similarly had lower 6-month mean VAS back pain scores than CMM patients (4.06 ± 2.46 versus 5.16 ± 2.67, respectively, adjusted $P = .008$ (adjusted as described for leg pain VAS, above) (Figure 4c). SCS patients had significantly lower back pain VAS scores at six months compared with baseline (4.06 ± 2.46 versus 5.45 ± 2.43, respectively, $P = .007$), while the CMM patients did not have significant improvements from baseline (5.16 ± 2.67 versus 4.48 ± 2.32, $P = .10$).

Figure 4. Pain outcomes for FBSS patients treated with SCS + CMM compared with CMM alone: data from one randomized controlled trial.

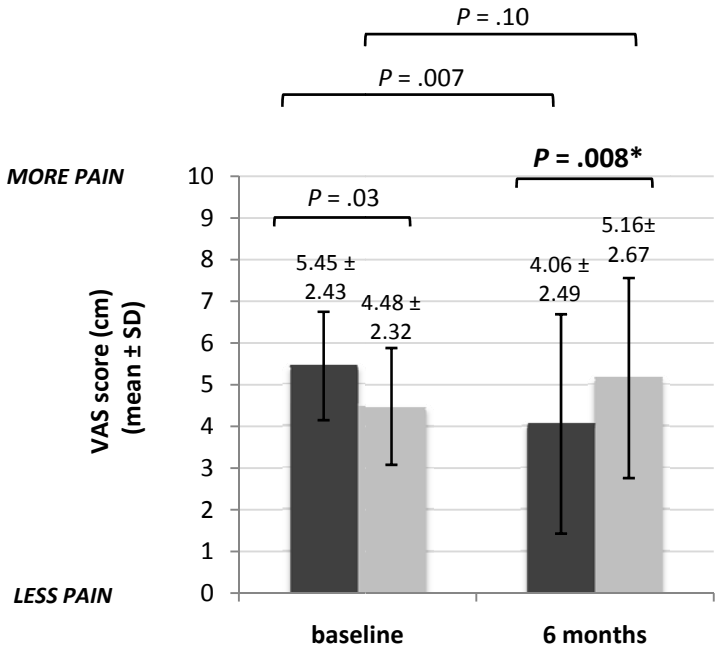
Leg pain relief compared with baseline (intention-to-treat analysis)[13]



b. Mean leg pain VAS scores (intention-to-treat analysis)[13]



c. Mean back pain VAS scores (intention-to-treat analysis)[13]



* p-value (but not scores) adjusted for baseline values and selected covariates (see text for details)

HR-QoL: SF-36 & EQ-5D (Figure 5)

Kumar et al. reported HR-QoL using two different outcome measures:

At six months, patients randomized to receive SCS + CMM had significantly better scores than did their CMM counterparts for seven of the eight SF-36 (Short-Form 36) outcome scales, which are outlined in Figure 5a. SCS + CMM patients had significant improvements in all but the role-emotion outcome scale compared with baseline, while CMM patients had significantly improved in only the general health outcome scale. The patient reported SF-36 health survey questionnaire does not provide a total score.

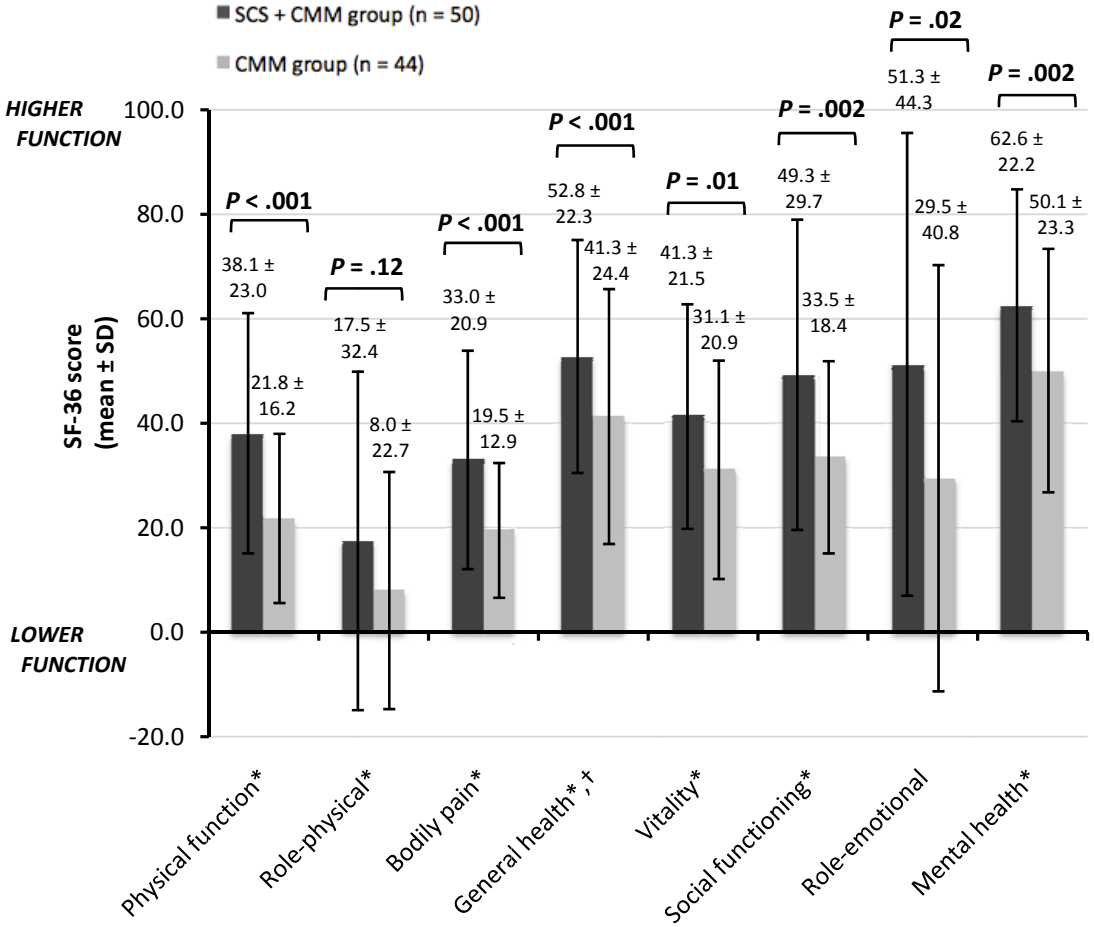
Manca et al. (2008)[69] reported that the six-month EQ-5D (EuroQol-5D) utility scores were significantly better in the SCS + CMM group compared with the CMM group, with a mean improvement of 0.23 (95% CI, 0.12, 0.35; $P < .001$) after adjusting in differences in baseline scores (Figure 5b). The utility scores were weighted against a large sample of the UK population.[69]

Functional capacity: ODI (Figure 6)

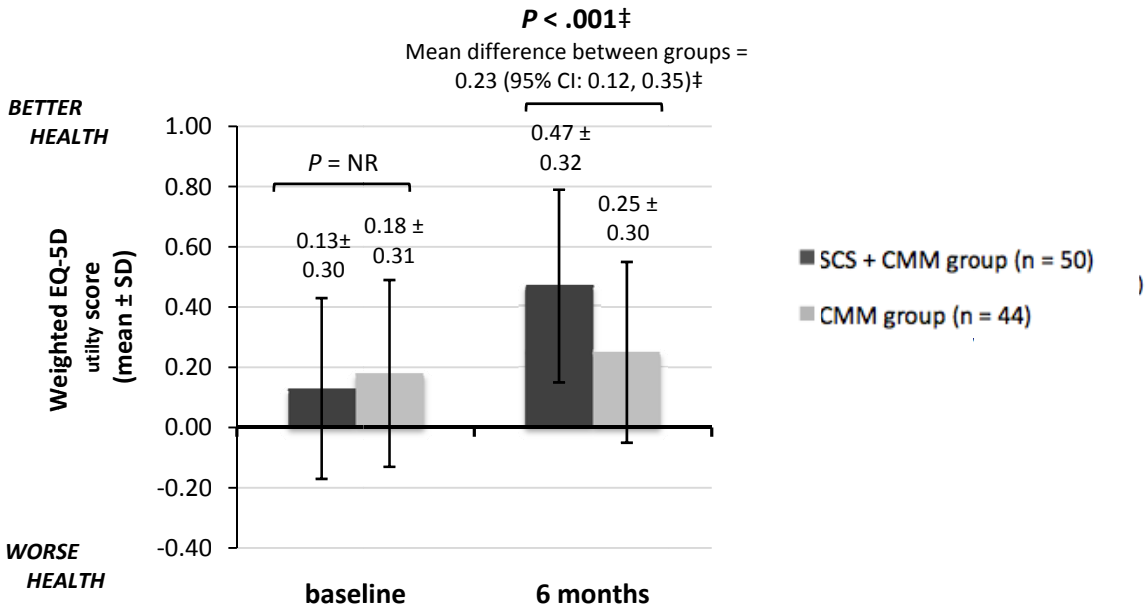
Patients randomized to receive SCS + CMM had significantly better functional capacity as measured by the patient reported Oswestry Disability Index (ODI) compared with those in the CMM group at six months ($P < .001$) (Figure 6).

Figure 5. Health-related quality of life (HR-QoL) outcomes for FBSS patients treated with SCS + CMM compared with CMM alone: data from one randomized controlled trial.

a. SF-36 scores at 6 months (intention-to-treat analysis)[13]

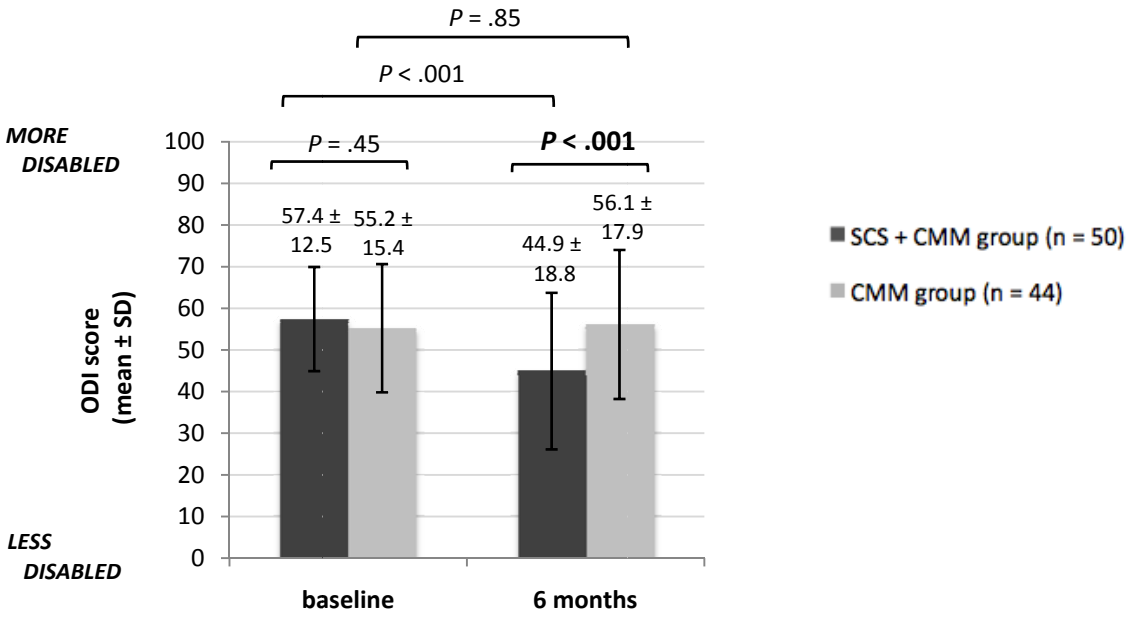


b. EQ-5D scores (intention-to-treat analysis)[69]



* SCS + CMM group scores were significantly better at six months compared with baseline (baseline scores NR):
physical function (P < .001); role-physical (P = .006); bodily pain (P < .001); general health (P = .004); vitality (P = .002); social functioning (P = .001); and mental health (P = .004).
† CMM group scores were significantly better at six months compared with baseline (baseline scores NR): general health (P = .007).
‡ adjusted for between-group differences in baseline scores

Figure 6. Functional capacity (ODI) outcomes for FBSS patients treated with SCS + CMM compared with CMM alone: data from one randomized controlled trial.[13]

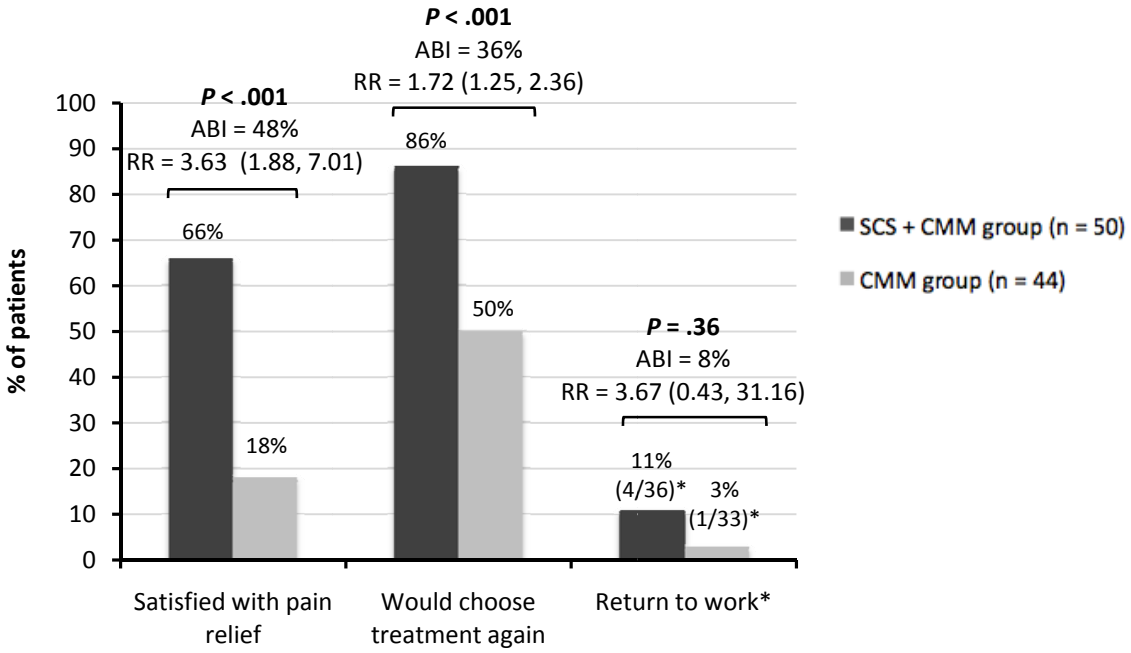


Patient satisfaction (secondary outcomes) (Figure 7)

Significantly more patients in the SCS + CMM group were satisfied with their pain relief at six months compared with those in the CMM group (66% versus 18%, respectively; absolute benefit increase, 48%; $P < .001$); the relative risk was 3.63 (95% CI, 1.88, 7.01) (Figure 7). Similarly, more SCS + CMM than CMM alone patients would choose their treatment again (86% versus 50%, respectively; absolute benefit increase, 36%; $P < .001$); relative risk, 1.72 (95% CI, 1.25, 2.36).[13]

There was no difference in the six-month return to work rate between groups (11% (SCS) versus 3% (CMM); absolute benefit increase, 8%; $P = .36$; relative risk, 3.67 (95% CI, 0.43, 31.16) (Figure 7). These rates were based only on those patients who were not working at baseline.[13]

Figure 7. Patient satisfaction outcomes for FBSS patients treated with SCS + CMM compared with CMM alone at six months: data from one randomized controlled trial.[13]



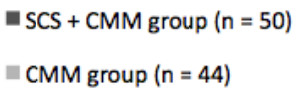
* Return to work calculations were based only on those patients not working at baseline.

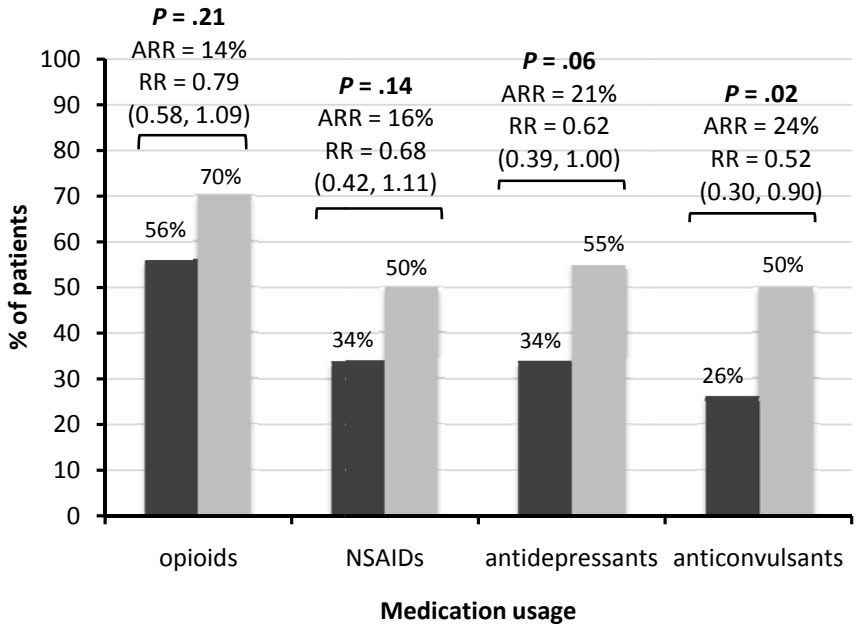
Medication usage (secondary outcomes)

At six months, there were no significant differences between the SCS + CMM and CMM groups in the percentage of patients using opioids (56% versus 70%, respectively; absolute risk reduction, 14%; *P* = .21; relative risk, 0.79 (95% CI, 0.58, 1.09), NSAIDs (34% versus 50%, respectively; absolute risk reduction, 16%; *P* = .14; relative risk, 0.68 (95 CI, 0.42, 1.11)), or antidepressants (34% versus 55%, respectively; absolute risk reduction, 21%; *P* = .06; relative risk, 0.62 (95% CI, 0.39, 1.00)). However, significantly fewer patients in the SCS group were taking anticonvulsants compared with their CMM counterparts (26% versus 50%, respectively; absolute risk reduction, 24%; *P* = .02; relative risk, 0.52 (95% CI, 0.30, 0.90)) (Figure 8). There were no significant within-group differences between medication usage at baseline compared to that at follow-up. Furthermore, there was no difference in the daily usage of morphine between groups (see Supplemental Table 3 for details).

There were no differences between groups in the percent of patients primarily using any of the following non-drug therapies: physical or psychological rehabilitation, acupuncture, or massage; significantly fewer patients in the SCS group were using TENS at six months compared with those in the CMM group (0% versus 5%, respectively, *P* = .02). Further details can be found in Supplemental Table 3.

Figure 8. Medication usage at six months for FBSS patients treated with SCS + CMM compared with CMM alone: data from one randomized controlled trial.[13]





North (2005)[14] (FBSS, continued)

Critical appraisal and overview

North et al., (2005)[14] conducted an RCT that evaluated the outcomes of FBSS patients treated with either SCS or reoperation. Sixty failed back surgery syndrome patients with leg pain that met or exceeded back pain were enrolled; patients were required to have nerve root compression amenable to reoperation and radicular pain that was nonresponsive to conservative treatment. Other details of the inclusion and exclusion criteria are outlined in Supplemental Table 2. Data were collected at a mean follow-up of 2.9 years (range, 1.8 – 5.7 years; standard deviation: 1.1 years)[13, 69], and the complete follow-up rate was 75%. Mean patient age was 50.2 years, and 50% of patients were male. The mean duration of chronic pain was not reported, but all patients were required to have persistent or recurrent radicular pain following at least one failed lumbosacral spine surgery[14].

Sixty FBSS patients were randomized to receive SCS (n = 30) or reoperation (n = 30). Only after randomization was complete did the authors obtain insurance authorization, and Workmen's compensation would not authorize treatment for nine patients. One other patient was excluded prior to treatment due to a stroke. Thus, 50 of the 60 patients randomized underwent treatment (SCS: 24/30; reoperation: 26/30). Trial SCS stimulation was conducted on all patients in the SCS group for a minimum of three days; all patients had an electrode

placed percutaneously and used an exernal stimulator. Patients who met all of the following criteria were considered to have had a successful trial: (1) at least 50% pain relief, (2) did not increase their analgesic medication dosage, and (3) had improved physical activity appropriate for their neurological status and age. Trial stimulation was successful in 71% (17/24), and these patients went on to receive permanent device implantation (two were lost prior to implantation). Of those patients (7/24) with unsuccessful trial stimulation, two dropped out of the trial, and the remaining five crossed over and received reoperation. Patients treated with reoperation underwent laminectomy and/or foraminotomy and/or discetomy with or without fusion and/or instrumentation. Postoperatively, all patients received physical therapy as well as analgesics, which were diminished as soon as possible. Cross-over was permitted after six months: in the SCS group, no additional patients had crossed over to reoperation (although 5/24 failed the trial stimulation and were considered to have crossed over); in the reoperation group, 54% (14/26) of patients crossed over to receive SCS (one other patient asked to cross-over but was unable to obtain insurance authorization). More details for patient numbers at each follow-up are reported in the table below as well as Supplemental Table 1.

Outcome measures included "success" (pain relief of at least 50% and patient satisfaction), improvement in activities of daily living, neurological status, and medication usage at final follow-up. Analyses included only those patients available at final follow-up; intention-to-treat analysis was performed for all outcomes, and "success" was evaluated several other ways (worst-case, per-protocol, treated as randomized, and analysis of crossovers only).[14]

This study received an LoE grade of II; details and rationale can be found in Appendix E. The primary limit of the study is the high cross-over rate (54%, 14/26) in the reoperation group after the six-month follow-up. Furthermore, the follow-up rate was only 75%; 15% (9/60) of randomized patients were lost prior to any treatment as their insurance providers would not authorize treatment. In addition, the study only compared SCS to reoperation, a treatment that had previously failed and is unlikely to improve outcomes in FBSS patients[11]. Workers' compensation were included in the study and consented to randomization at the same rate as other patients, but had a significantly lower rate of SCS treatment ($P < .01$) because they were less likely to receive third-party authorization for treatment. Of the patients who were randomized to receive SCS, 40% (24/60) were receiving workers' compensation; 30% (15/50) of those treated with SCS were receiving workers' compensation. Randomization was achieved using computer-generated random assignments obtained from an independent biostatistician; concealment was ensured with consecutive, numbered, sealed, and opaque envelopes. Due to the nature of the treatments, blinding of patients and investigators was not possible. Baseline characteristics were not robustly described for each treatment group. Outcomes were analyzed according to the intention-to-treat principle. This RCT was also funded by Medtronic, Inc.; furthermore, the hospital at which the study was conducted (Johns Hopkins) received profits from a sale of a company to Medtronic, Inc.

The following table provides patient numbers available for follow-up for each treatment and data collection point:

	SCS (n = 30 randomized)		Reoperation (n = 30 randomized)	
	Implant received	**No implant (cross-over)***	**Reoperation**	**Crossed over**
Initial treatment	n = 17	n = 5	n = 26	-
Treatment at six months	n = 16	n = 5	n = 26	-
Treatment at final follow-up (mean 2.9 years)	n = 15	n = 4	n = 12	n = 14

* Except for SCS patients that failed trial stimulation, cross-over was permitted AFTER 6 months.

The following outcomes were evaluated:

"Success": pain relief ≥ 50% AND patient satisfaction (Figure 9)

The outcome measure by which pain was measured was not disclosed; patient satisfaction was evaluated by asking patients whether they would go through the treatment again given their experience so far.

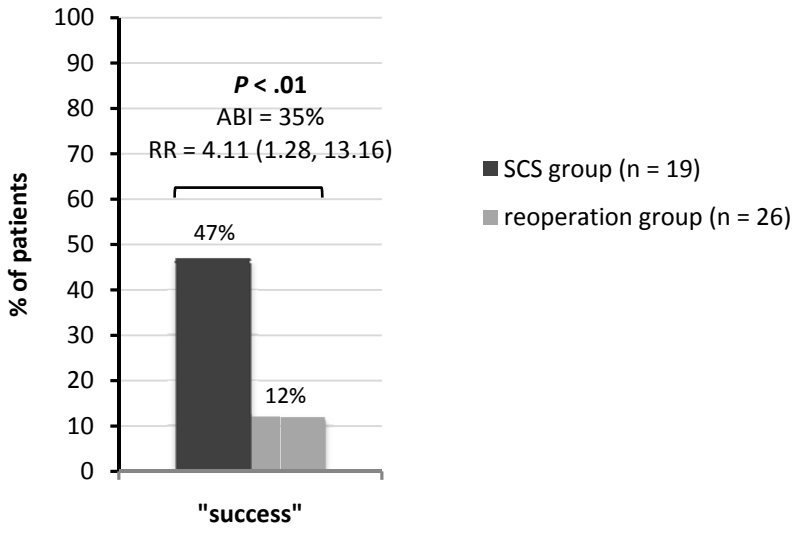
Intention-to-treat analysis: At long-term (2.9 ± 1.1 years) follow-up, significantly more patients in the SCS than in the reoperation group had achieved "success", which was defined by at least a 50% reduction in pain and patient satisfaction. Of those available for follow-up, 47% (9/19) in the SCS group and 12% (3/26) in the reoperation had achieved "success" ($P <$ .01; absolute benefit increase, 35%; relative risk, 4.11 (95% CI, 1.28, 13.16)) (Figure 9)[14].

"Worst-case" analysis: "Worst case" analysis assumed that those lost to follow-up were failures, and again showed that significantly more patients in the SCS group achieved "success" compared with those in the reoperation group at final follow-up (SCS: 39% (9/23) versus reoperation: 12% (3/26); relative benefit increase, 27%; $P = .04$)[13].

Per-protocol analysis: Similar results were obtained by a per-protocol analysis, which analyzed patients according to the treatment received at final follow-up. Significantly more patients last treated with SCS (52% (15/29)) than with reoperation (19% (3/16)) achieved "success" ($P < .05$; relative benefit increase, 33%)[14].

Treated as randomized versus crossovers: Of those patients randomized to receive SCS and available at final follow-up, 15/24 were last treated with SCS while 4/24 underwent reoperation (due to failed trial stimulation). The rate of success in those treated with SCS was 60% and in those treated with reoperation was 0% (relative benefit increase, 60%). Similarly, of patients randomized to receive reoperation, 12/26 were last treated as randomized, while 14/26 crossed over to receive SCS. The success rate in patients last treated with reoperation was 25%, while 43% of patients who crossed to SCS achieved "success" (relative benefit increase, 18%). Significantly more of those who crossed over to SCS were successful at long-term follow-up than those who crossed over to reoperation (again, 43% versus 0%, respectively; relative benefit increase, 43%; $P < .01$).

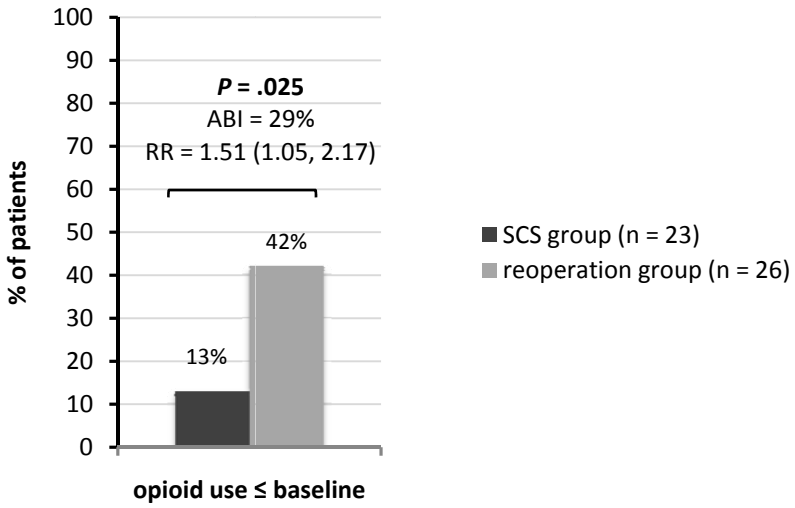
Figure 9. "Success" in FBSS patients treated with SCS compared with reoperation alone at a mean of 2.9 years: data from one randomized controlled trial (intention-to-treat analysis).[14]



Medication usage

At final follow-up, significantly more patients in the SCS group were taking a stable or decreased dose of opioid medications compared with baseline than those in the reoperation group (87% versus 58%, respectively; absolute benefit increase, 29%; *P* = .025; relative risk, 1.51 (95% CI, 1.05, 2.17)) (Figure 10). Medication dosages were not reported.

Figure 10. Opioid use in FBSS patients treated with SCS compared with reoperation alone at a mean of 2.9 years: data from one randomized controlled trial (intention-to-treat analysis).[14]



Activities of daily living and neurological status

The authors reported no significant differences between groups in ability to perform daily activities (work, walk, climb stairs, sleep, engage in sex, drive a car, sit at a table to eat, and medication use) or neurological status (lower extremity strength and coordination, sensation, bladder/bowel function) at final follow-up, however, raw data were not provided.

4.1.2. Effectiveness

Failed back surgery syndrome (FBSS) (workers' compensation setting)

Turner (2010)[75]

Critical appraisal and overview
Turner et al., (2010)[75] recently conducted a prospective cohort study on FBSS patients who had open workers' compensation claims with the state of Washington. This work was commissioned by the Washington State Department of Labor and Industries (DLI), which administers the workers' compensation program, and conducted by the University of Washington. Patients were treated with SCS, Pain Clinic (PC), or Usual Care (UC). The treatment plans and protocols were determined by the physician, and treatment details were not provided. All patients had leg pain exceeding back pain; further details of the inclusion and exclusion criteria are outlined in Supplemental Table 2. Data were analyzed with a modified per-protocol analysis according to the last treatment received during the first year of the study. Some data for the SCS and PC groups were additionally analyzed using a per-protocol analysis according to the final treatment received (ie., permanent SCS implants (SCS) or at least some pain clinic treatment (PC)). A total of 159 patients were enrolled, and 6, 12, and 24 month data were reported using the patients with complete follow-up (155/159, 148/159, and 138/159 at each follow-up, respectively). Of patients that complete the study, mean age was 44.1 years, and 77% were male. The mean duration of chronic pain was 38 months, and was significantly longer in the SCS group than in the PC group ($P < .02$)[75].

There were 52 patients enrolled to receive SCS; 5 did not undergo an SCS trial, and an additional 4 patients were gained due to cross-over from UC (n = 3) or PC (n = 1). Of the 51 patients who underwent trial stimulation, 53% (27/51) went on to receive permanent SCS implants. Details of the trial stimulation were not reported. Notably, a lower percentage of patients in the SCS group received permanent implants (53%) compared to the two RCTs on FBSS patients (71–83%)[13, 14]. After loss to follow-up, 43 patients (of the 51 treated) were included in the 24 month analysis. In the pain clinic (PC) group, 51 patients were enrolled; 17 did not undergo any PC services and crossed to a different group, one patient was excluded after receiving SCS treatment outside of the study, and an additional 6 patients were gained due to cross-over from SCS (n = 2) or UC (n = 4). The 24 month analysis included the 34 (of the 39 treated) patients available for follow-up. The usual care (UC) group originally enrolled 56 patients; 7 crossed to other groups, and 19 were gained due to cross-over from SCS (n = 3) or PC (n = 16). Seven patients were lost to follow-up, thus the UC group was comprised of 61 patients in the 24 month analyses. Additional details for patient numbers at each follow-up are reported in Supplemental Table 1.

A companion report was recently published by Turner et al (2010)[76]. While waiting for final data availability needed to make a coverage decision, DLI decided to authorize SCS for patients who met the eligibility requirements. During the ten-month enrollment period, a total of 30 patients underwent at least trial stimulation. This second cohort of patients (SCS2) had similar baseline characteristics to those patients that comprised the SCS group in the original

study[75], except that SCS2 patients had worse mental health scores, better leg pain intensity, and were all male. Both groups had comparable rates of successful trial stimulation (SCS: 53%; SCS2: 57%). At twelve months' follow-up, the SCS2 group had similar outcomes to the original SCS group, except more patients in the SCS2 group used opioids on a less than daily basis (13% versus 38% in SCS2; $P < .05$).

The primary outcome was "success", defined by the following criteria: (1) leg pain relief of ≥ 50% (compared to baseline); (2) ≥ 2-point improvement on the 24-point Roland-Morris Disability Questionnaire (RDQ); and (3) opioid use on a less than daily use (< 28 days per month). The authors noted that recent evidence suggests that pain relief of at least 30% could be considered clinically meaningful, while pain relief of 50% or more would be considered substantial. Similarly, a 5-point improvement on the RDQ may be needed to reflect a clinically important improvement[13, 14]. Thus "alternative success" was reported, and was defined by the following criteria: (1) leg pain relief of ≥ 30% (compared to baseline); (2) ≥ 5-point improvement on the 24-point Roland-Morris Disability Questionnaire (RDQ); and (3) opioid use on a less than daily use (< 28 days per month). Data for many of these components were also reported separately. Other outcomes reported included back pain intensity, SF-36 scores, ability to perform daily activities, medications and other treatments used for pain, as well as work status and disability.

The results of this study apply to a workers' compensation population with an open compensation claim in the State of Washington. Worker's compensation patients tend to differ in socioeconomic characteristics compared with patients not receiving worker's compensation[77]. Furthermore, workers' compensation patients have worse pain outcomes compared with other patients[78, 79].

This study received an LoE grade of II; details and rationale can be found in Appendix E. This was a well conducted cohort study. However, the potential for selection bias is a threat to validity in any cohort study and is a limitation. In the present study, patients in the SCS group may be different from those in the other treatment groups in important ways undetected by the investigators, ways that may affect outcomes. . For example, patients in the SCS group tended to have more legal representation, longer duration of work time loss compensation, longer duration of leg pain and greater leg pain intensity compared with those in the pain clinic or usual care groups. These differences suggest that the SCS group differs from the control groups in potentially important ways.

While the study was not funded by a device manufacturer, it was commissioned by Washington State Department of Labor and Industries, which administers the workers' compensation program.

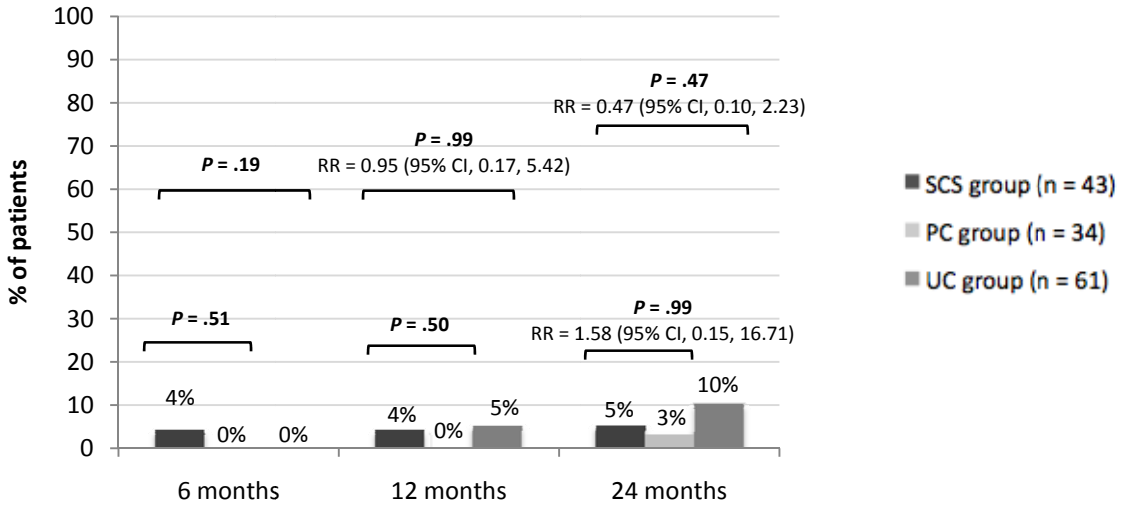
The following outcomes were evaluated:

"Success": leg pain relief ≥ 50% , RDQ improvement of ≥ 2 points, and less than daily opioid usage (Figure 11)

Less than 10% of patients in any group achieved the primary outcome of "success", and there were no significant differences in the percentage of patients achieving this outcome between the SCS, PC, and UC groups at any follow-up (see Figure 11 for data).

Four percent of patients in the SCS group achieved the alternate definition of success (leg pain relief ≥ 30%, RDQ improvement of ≥ 5 points, and less than daily opioid usage) at six months; no information was provided for the PC or UC groups. There were no significant differences between the SCS and PC or UC groups in the rate of achieving the alternate success criteria at the 12 or 24 month follow-ups (data not reported).

Figure 11. "Success"* in FBSS patients treated with SCS compared with pain clinic (PC) or usual care (UC) at 6, 12, and 24 months: data from one prospective cohort study.[75]

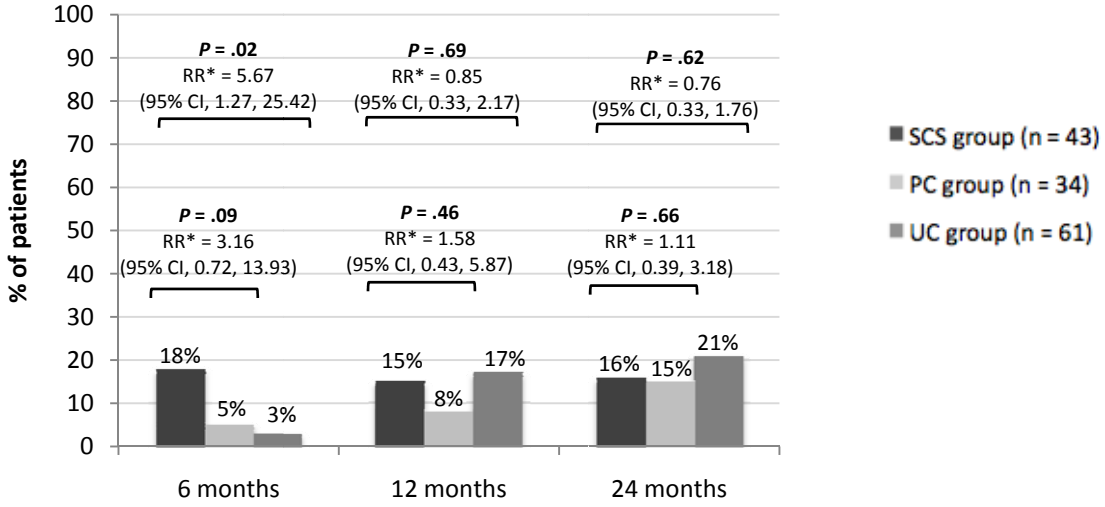


*Success is defined by leg pain relief ≥ 50%, RDQ improvement of ≥ 2 points, and less than daily opioid usage

Leg pain relief ≥ 50% (Figure 12)

At six months, significantly more SCS achieved leg pain relief of at least 50% compared with patients in the UC group (18% versus 3%, respectively; *P* = .02), but the difference between the SCS and PC groups was not statistically meaningful (18% versus 5%, respectively; *P* = .09). By 12 and 24 months, the differences were no longer statistically significant, as the control groups had improved rates of pain relief (see Figure 12 for data).

Figure 12. Leg pain relief ≥ 50% in FBSS patients treated with SCS compared with pain clinic (PC) or usual care (UC) at 6, 12, and 24 months: data from one prospective cohort study.[75]



* crude (unadjusted) estimates

The authors also noted that the clinically meaningful difference may in fact be pain relief of at least 30% (instead of 50%)[68]. Similar to the alternate definition of success, there were no statistically significant differences between the SCS and PC or UC groups at the 12 or 24 month follow-ups (data not reported).

Other outcomes

Mean leg or back pain scores obtained using numerical rating scales were similar in all three groups at all follow-ups (see Supplemental Table 3 for details).

There were no significant differences between treatment groups in several other outcomes, which included quality of life (as measured by the SF-36), function (as measured by the Roland-Morris Disability Questionnaire, ability to perform daily tasks, work/disability status, and mean time lost from work), and medication usage (with the exception of daily opioid use, which was significantly lower in the SCS versus the PC (but not the UC) group at 6 months only (SCS: 12%; PC: 34%; $P = .04$ as well as anticonvulsant use, which was higher in the SCS than the PC (but not the UC) group (SCS: 33% versus PC: 6%; $P < .01$)). According to per-protocol analysis, patients who received permanent SCS implants had significantly lower rates of surgery (other than SCS) at one year than those who underwent at least some Pain Clinic therapy (0% (0/27) versus 19% (4/21), $P = .03$). In addition, SCS patients with permanent implants had lower rates of physical therapy (33% (SCS) versus 95% (PC) $P < .001$), occupational therapy (7% versus 81%, respectively, $P < .001$), and psychological therapy (7% versus 52%, respectively, $P = .001$) at one year than their PC counterparts, although no differences between these groups were found in the rate of use of other alternative therapies (spinal injection, massage, back brace/corset, ultrasound, and

bedrest). Further details can be found in Supplemental Table 3. When considering all the patients in each treatment group, a lower percentage of SCS patients had undergone a variety of other pain treatments at one year compared with the PC and/or UC groups, although the authors did not report statistical significance (p-values): (1) surgery (other than SCS): SCS (8%, 4/51) versus PC (21%, 8/38); (2) physical therapy: SCS (24%, 12/51) versus PC (74%, 28/38) and UC (39%, 26/66); (3) occupational therapy: SCS (10%, 5/51) versus PC (53%, 20/38); (4) psychological therapy: SCS (22%, 11/51) versus PC (39%, 15/38); and (5) ultrasound: SCS (4%, 2/51) versus UC (21%, 14/66). Patients in the SCS group had more frequent back brace/corset usage (31%, 16/51) compared with patients in the PC group (16%, 6/38). Little differences (< 10%) were found in the usage of other treatments between the SCS and other groups, including surgery, occupational therapy, back brace/corset, and psychological therapy (SCS versus UC); ultrasound (SCS versus PC); as well as spinal injection, massage, and bedrest (SCS versus both comparators).

Differences between RCTs and cohort study

The results between the randomized controlled trials[13, 14, 69, 74] evaluated in this HTA were different than the results in the prospective cohort study[75]. Several potential reasons for these differences include the following:

1. In cohort studies, unknown characteristics unevenly distributed among treatment groups may confound results and influence the assessment of effectiveness (selection bias). Random assignment tends to minimize the threat from this kind of bias, and this, in part, may explain some of the difference.
2. Cohort studies and randomized controlled trials frequently apply to different patient populations. For example, the cohort study by Turner et al[75] was conducted among patients on workers' compensation while the RCTs treated a minority of compensation patients. Pain outcomes have been shown to be worse among workers' compensation patients compared with patients not on workers' compensation[78, 79].
3. In RCTs the treating physicians are often selected based on expertise and experience that may be atypical of physicians in general[80]. This may have been the case across the studies included in this HTA with patients in the cohort study receiving SCS at the hands of providers with wide-ranging skill and experience.
4. Psychological screening of patients prior to treatment, which is required for coverage by CMS and at least some other third-party payers (Table 2), differed between studies. While all three RCTs[13, 14, 25] excluded patients with a major psychiatric condition (see supplemental Table 2) and conducted psychological screening of all patients at baseline, the cohort study[75] left psychological screening up to the treating physician (25% (13/51) of patients in the SCS group underwent such screening) and did not list major psychiatric disorders in the exclusion criteria. However, the cohort study did report statistically similar SF-36 Mental Health baseline scores between the three treatment groups.
5. Sponsorship of the RCTs and the cohort study provide a further reason that may partially explain the difference in results. Both of the RCTs evaluating FBSS were funded by a device manufacturer, while the cohort study evaluating FBSS was funded by a state department that administers a workers compensation program[14, 74]. Industry support has been shown to correlate with reporting of better outcomes compared with no industry support[81-83]. In one trial on FBSS, the principal investigator from Johns

Hopkins University received a share of the proceeds from the sale, and Medtronic provided funding for the study[14]. The second trial was funded and managed in part by Medtronic, who additionally collected and analyzed the data[13]. Funding for the cohort study came from Washington State Department of Labor and Industries, which funds the workers' compensation program for the state of Washington[75]; the study reported that all patient-reported data collection, data analyses, and report writing were performed independently of the Department of Labor and Industries.

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

One RCT provided data on the short-term efficacy of SCS compared with physical therapy in complex regional pain syndrome (CRPS) patients. Two RCTs reported on the efficacy of SCS in patients with failed back surgery syndrome (FBSS): one RCT provided data on both the short- and mid-term efficacy of SCS and conventional medical management (CMM) compared with CMM alone, while another provided data on the short-term efficacy of SCS compared with lumbar reoperation. Heterogeneity between these studies prevented pooling of the data. In general, the RCTs reported significantly improved outcomes in the short-term for patients randomized to receive SCS than those randomized to the control groups; however, results were mixed at the mid-term follow-up in the one RCT reporting results after five years.

One prospective cohort study provided data on the short-term effectiveness of SCS compared with Pain Clinic and Usual Care treatments in FBSS patients with open workers' compensation claims in the State of Washington. In general, the cohort study found no differences in outcomes between patients in the SCS and two control groups.

"Success" from a composite score
Efficacy: One RCT found that patients randomized to receive SCS had significantly improved "success" (a composite of pain relief and patient satisfaction) compared with those randomized to undergo lumbar reoperation at mean of 2.9 years follow-up.

Effectiveness: The prospective cohort study on workers' compensation patients found no difference between SCS, pain clinic (PC), or usual care (UC) groups at any follow-up up to 24 months in the percent of patients achieving the primary outcome composite measure of success (includes pain, function, and medication usage components).

Pain relief
Efficacy: Patients randomized to receive SCS had significantly improved pain relief compared with those randomized to undergo control treatments in two RCTs with ≤ 2 year follow-up. One of these RCTs reported that the differences between groups in both the change in VAS scores (from baseline) and in mean VAS scores were no longer statistically significant by three to five years post-implantation.

Effectiveness: The prospective cohort study on workers' compensation patients reported that significantly more patients in the SCS group achieved ≥ 50% leg pain relief by six months than those in the UC group, there was no difference between the SCS and PC group at the same follow-up; furthermore, no differences were identified between groups in the percentage of patients achieving leg pain relief of ≥ 50% or more at the 12- and 24-month follow-ups.

Function

Efficacy: One RCT found that patients in the SCS group had significantly better Oswestry Disability Index scores than those in the CMM group at six months follow-up. Another RCT reported no significant differences between the SCS and reoperation groups in the neurological status or ability to perform daily activities a mean of 2.9 years follow-up, however, raw data were not provided.

Effectiveness: There were no significant differences in either the Roland-Morris Disability Questionnaire (RDQ) scores or ability to perform daily tasks between treatment groups in the prospective cohort study on workers' compensation patients.

Health-related quality of life (HR-QoL)

Efficacy: One RCT reported no difference in several QoL outcome measures between the SCS and physical therapy groups, including the mean percent change in quality of life at the 6- and 24- month follow-ups as well as the Nottingham Health Profile, EQ-5D (EuroQol-5D), and Self-Rating Depression Scale scores at five years. Another RCT reported that patients randomized to receive SCS had significantly better scores in seven of the eight SF-36 (Short-Form 36) outcome scales compared with those randomized to receive CMM at six months. The same RCT reported that the six-month EQ-5D utility scores were significantly better in the SCS compared with the CMM group. Further, no difference was found between groups in the rate of patients (not working at baseline) who had returned to work by six months.

Effectiveness: The prospective cohort study on workers' compensation patients reported no significant differences between treatment groups in SF-36 scores and work/disability status.

Patient satisfaction and perceived effect

Efficacy: One RCT reported that significantly more patients in the SCS group were satisfied with both their level of pain relief and with their treatment in general than those in the CMM group at six months follow-up. Another RCT incorporated patient satisfaction with pain relief into a composite outcome, "success", which was reported above. Another RCT reported global perceived effect (GPE) scores. Significantly more patients in the SCS group reported GPE of "much improved" or "best ever" at both the 6- and 24- month follow-ups compared with the physical therapy group; however the differences between groups were no longer statistically significant by five years.

Medication usage

Efficacy: One RCT reported no differences at six months between the SCS and CMM groups in the percentage of patients using opioids, non-steroidal anti-inflammatory medications, or antidepressants; however, significantly fewer SCS patients were taking anticonvulsants than those in the CMM group. There were no differences between the SCS and CMM groups in the

percentage of patients using all reported non-drug therapies (eg., physical or psychological rehabilitation, acupuncture, or massage) except for TENS (transcutaneous electrical nerve stimulation), for which the rate of use was lower in SCS compared with CMM patients. Another RCT found that significantly more patients in the SCS group were taking a stable or decreased dosage of opioids (versus baseline) than those in the reoperation group at a mean of 2.9 years follow-up.

Effectiveness: Although significantly fewer patients in the SCS group used opioids on a less than daily basis than did those in the PC group at six months, no other significant differences between treatment groups were identified in the prospective cohort study on workers' compensation patients.

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

We present safety information in three sections: revisions of SCS devices, other SCS-related complications, and non-SCS related complications. We stratified complications by follow-up period: short-term = 1 to <5 years, mid-term = 5 to <10 years, and long-term = >10 years. Short-term data are presented from available comparative studies, while mid-term data are presented from one comparative study and available case series. We found no long-term data.

4.2.1. Revision of SCS devices

Short-term follow-up: comparative studies

All three RCTs and the one cohort study reported short-term (< 5 years) revision rates of SCS devices. However, each study reported the data differently, and not all studies reported an overall revision rate (the proportion of patients who underwent one or more revision). Therefore, revision rates were difficult to pool. Briefly:

- Kemler (2000, 2004, 2008)[25, 71, 72]:
  - Patient basis: SCS group only, permanent implant received
  - Denominator used for complication rates: n = 24 (though follow-up rates ranged from 83 – 100%); Kumar (2004, 2008)[71, 72] only use the number of revisions when reporting rates for revision of specific SCS components

- Kumar (2007)[13] (12 month f/u):
  - Patient basis: all patients receiving SCS (including crossovers), any implant received (including trial stimulation)
  - Denominator used for calculations: n = 84 (all treated; though only 71/84 were available at the 12-month f/u)

- Kumar 2008[74] (24 month f/u):
  - Patient basis: SCS group only, any implant received (including trial stimulation)
  - Denominator used for calculations: n = 42 (based on number of patients available at 24-month f/u, though 52 patients received treatment)

- North 2005[14]:
  - Patient basis: all patients receiving SCS (including crossovers), permanent implant received
  - Denominator used for calculations: n = 31 (all treated; though only 29/31 were available at long-term f/u)

- Turner 2010[75]
  - Patient basis: all patients receiving SCS (including crossovers), permanent implant received
  - Denominator used for calculations: n = 27 (all treated; the number of patients with permanent implants available at follow-up was not reported; data available through 18 months follow-up)

Data can be summarized as follows, additional details can be found in Table 6:

- Overall short-term revision rates ranged from 25 to 38% of patients (ie., 25 to 38% of patients had one or more revisions for any cause unless otherwise stated) as reported by two RCTs (each with two different follow-ups)[13, 25, 71, 74]. In some studies, the overall percentage of patients that underwent revision was not reported.
- Electrode revision:
  - Electrode repositioning due to migration or improvement of paresthesia: 10 to 21% of patients as reported by three RCTs (one with two different follow-ups) and one cohort study[13, 14, 25, 74, 75]; 36% of revisions as reported by one RCT[71].
  - Electrode replacement: 4 to 9% of patients as reported by one RCT[25, 71] (with two different follow-ups).
- Generator revision:
  - Revision or replacement due to painful pulse generator pocket, migration, or unreported cause: 1 to 11% of patients as reported by two RCTs (one with two different follow-ups)[13, 25, 74] and one cohort study[75]; 36% of revisions as reported by one RCT[71].
- Total removal (and replacement) of SCS system:
  - Removal and replacement of system due to local infection: 3–4% of patients as reported by two RCTs (one with two different follow-ups)[14, 25, 71].
  - Total removal of system without replacement due to recurrent rejection, infection, discomfort, ineffective pain relief, and/or seizures: 8–22% of patients as reported by one RCT[71] and one cohort study[75].
- Additional revisions were performed for the following reasons in one RCT (with two different follow-ups)[13, 74] (details of the revisions were not reported):
  - Loss of therapeutic effect, loss of or unpleasant paresthesia: 1–5% of patients
  - Technique: 5% of patients (see Table 6 for details)
  - Biological: 7% of patients, including infection or wound breakdown in 5–6% of patients and pain at the generator incision site in 1–2% of patients.

Table 6. Short-term revision rates* (%) from RCTs

Author (Year)	Mean F/U (years) (range)	# patients with perm. SCS implants	Preoperative diagnosis (N, %)	Overall revision rate	Reason for revision
Kemler (2000)	0.5 (no range)	N = 24†	CRPS-I (100%)	25% (6/24) of patients† (11 events)	**Revision of electrode: (summary rate NR)** • repositioning of electrode to improve placement: 21% of all patients • defective electrode: 4% **Revision of generator: 8% of patients** • painful pulse generator pocket: 8% of all patients **Revision of connecting cable/lead: NR** **Total removal and replacement of system: 4% of patients** • infection: 4% of all patients
Kemler (2004)	2 (no range)	N = 24†		38% of patients† (9/24) (22 events)	**Revision of electrode: 45% of revisions (10/22) (number of patients NR)** • repositioning of electrode (cause NR): 36% of revisions (8/22) • replacement of electrode: 9% of revisions (2/22) **Revision of generator: 36% of revisions (8/22) (number of patients NR)** • painful pulse generator pocket: 32% of revisions (7/22) • replacement of generator: 5% of revisions (1/22) **Revision of connecting cable/lead: NR** **Total removal of system: 9% of revisions (2/22) (8% of patients)** • recurrent rejection: 5% of all patients • relapsing ulcerative colitis caused by system: 5% of all patients **Total removal and replacement of system: 5% of revisions (1/22) (4% of patients)** • infection: 4% of all patients
Kumar 2007	1.0 (no range)	N = 84‡ (includes cross-over)	FBSS (100%)	24% of patients‡ (20/84)	**Hardware-related: 12% (10/84) of patients** (number of events NR) • Electrode migration: 10% of all patients • Electrode/extension fracture/torqued contacts: 1% • Generator migration: 1% **Loss of therapeutic effect, loss of or unpleasant paresthesia: 1% (1/84) of patients** (details of revision NR) (number of events NR) **Technique**: 5% (4/84) of patients** (5 events) **Total biological: 7% (6/84) of patients** (number of events NR) • Infection/wound breakdown: 6% of all patients • Pain at incision site for generator: 1%

Author (Year)	Mean F/U (years) (range)	# patients with perm. SCS implants	Preoperative diagnosis (N, %)	Overall revision rate	Reason for revision
					• Fluid collection at neurostimulator pocket: 0%
Kumar 2008	2.0 (no range)	N = 42††		31% of patients†† (13/42)	**Hardware-related: (summary rate NR)** • Electrode migration: 14% of all patients • Electrode/extension fracture/torqued contacts: 2% • Generator migration: 2% **Loss of therapeutic effect, loss of or unpleasant paresthesia: 5% (2/42) of patients** (details of revision NR) **Technique‡‡: 5% (2/42) of patients** **Total biological: 7% (3/42) of patients** • Infection/wound breakdown: 5% of all patients • Pain at incision site for generator: 2% • Fluid collection at neurostimulator pocket: 0%
North 2005	2.9 ± 1.1 (1.8–5.7)	N = 31***	FBSS (100%)	NR	**Revision of electrode: 10% of patients (3/31)** • displaced or mispositioned electrode: 10% of all patients **Revision of generator: NR** **Revision of connecting cable/lead: NR** **Total removal and replacement of system: 3% of patients (1/31)** • infection: 3% of all patients
Turner 2010	1.5 (no range)	N = 27	FBSS (100%)	NR	**Revision of electrode/lead: 15% of patients (4/27)** • Lead migration or malpositioning/ineffective or decreased pain relief **Revision of generator: 11% of patients (3/27)** • Pain/discomfort at generator site **Revision of connecting cable/lead: NR** **Total removal and replacement of system: 4% (1/27), due to:** • Lead migration and "SCS malfunction" **Total removal of system: 22% of patients††† (6/27), due to:** • ineffectiveness and discomfort (20 months post-implantation)††† • deep abscess over generator; device had to be removed and patient did not have re-implantation • ineffectiveness of pain relief (10 months post-implantation) • discomfort and ineffectiveness (16 months post-implantation) • seizures and ineffective pain relief (8 months post-implantation) • pain at pulse generator site and decreased effectiveness (17 months post-implantation)

Author (Year)	Mean F/U (years) (range)	# patients with perm. SCS implants	Preoperative diagnosis (N, %)	Overall revision rate	Reason for revision

* Additional details can be found in Supplemental Table 4.
†Kemler: safety data reported on all patients randomized to receive SCS that underwent permanent implants. In Kemler 2004, 22/24 patients were available for follow-up; all patients were available for follow-up in Kemler 2000.
‡ Kumar 2007: safety data reported on all patients that received electrodes, including those that only underwent trial stimulation and as well as those randomized to CMM alone who crossed over (or attempted to cross over). Only 71/84 patients were available at follow-up.
** Kumar 2007: Technique-related complications include: pulse generator cap not installed when only one lead was implanted; intermittent stimulation due to improper connection of extension to pulse generator; shocks caused by anteriorly implanted electrode; lead cut during implantation; and dural tear during implantation.
†† Kumar 2008: safety data reported on all patients that received that were randomized to SCS and available for follow-up (42/52).
‡‡ Kumar 2008: Technique-related complications included intermittent stimulation due to improper connection of extension to pulse generator; shocks caused by anteriorly implanted electrode; and lead cut during implantation.
*** North 2005: safety data reported on all patients that underwent permanent SCS implants, including crossovers. Only 29/31 were available at long-term follow-up.
††† Turner 2010: study reported that 19% (5/27) of patients underwent total explantation of system, but another patient was apparently not included in this total and had explantation 20 months after the original implantation; our rate includes this additional patient.

Mid-term follow-up: comparative studies and case series

Mid-term (5 to < 10 years) revision rates of SCS devices were reported by one RCT[72]. In addition, we identified six case series[84-89] with a mean follow-up of at least five years; it is important to note that there was a wide range of follow-ups in these case series, which makes the data somewhat difficult to interpret.

Again, the RCT reported revision rates based only on those patients randomized to receive SCS who underwent permanent device implantation. Rates from case series are based on the number of patients who underwent permanent SCS implantation.

Data can be summarized as follows, additional details can be found in Table 7:

- The RCT[72] reported a revision rate of 42%. This rate does not include the 54% of patients who underwent 17 pulse generator replacements; a total of 42 generators were needed in five years of treatment (mean battery life of 4 years based on all 36 randomized patients).
- One case series[84] reported an overall revision rate of 60% at a mean of 5.2 years follow-up (range, 1 to 13 years). The other five case series did not provide total revision rates.

- Electrode revision:
    - RCT: Electrode revision accounted for 59% of all revisions[72] by the five year follow-up. These revisions included electrode repositioning and replacement (38% and 21% of all revisions, respectively). Patient rates were not reported.
    - Case series: Electrode revision was necessary in 3% of patients in one case series[89], 7.4% of all systems in another[88], and accounted for 44% of all revisions in a third case series[84]. Reasons for revision include the following:
        - Inappropriate area of paresthesia: 14% of all revisions as reported by one case series[84]
        - Fibrosis causing inadequate paresthesia: 11% of all revisions as reported by one case series[84]
        - Inadequate paresthesia due to unknown cause: 7% of all revisions as reported by one case series[84]
        - Infection: 1% of all revisions as reported by one case series[84]
        - Displaced electrode: 3–33.5% of patients as reported by three case series[85, 86, 89]; 11% of all revisions as reported by one case series[84]
        - Fractured electrode: 3.6–6.4% of patients as reported by two case series[85, 86] (Kumar 2007, 1998)
        - Hardware malfunction: 3.6–6.0% of patients as reported by two case series[85, 86]; 7.4% of all systems due to electromechanical failure as reported by one case series[88]

- Generator revision:
    - RCT: Generator revision (but not replacement) due to a painful pulse generator pocket accounted for 28% of all revisions[72] by the five year follow-up. Patient rates were not reported.
    - RCT: Generator replacement was necessary in 54% of patients (17 procedures)[72] by the five year follow-up due to battery depletion and other causes.
    - Generator revision was necessary in 5.4% of all systems in one case series[88], and accounted for 30% of all revisions in a second[84]. Reasons for revision include the following:
        - Battery depletion: 22% of all revisions as reported by one case series[84]
        - Discomfort: 6% of all revisions as reported by one case series[84]; 1.5% of patients as reported by one case series[86]
        - Defective generator: 1% of all revisions as reported by one case series[84]
        - Displacement due to pregnancy or improper placement: 1% of all revisions as reported by one case series[84]; 1.2% of patients as reported by one case series[86]
        - Electrical leak: 1.2% of patients as reported by two case series[85, 86]
        - Failure: 5.4% of systems as reported by one case series[88]
- Revision of connecting cable/lead:
    - Revision of the cable connecting the electrode to the generator was necessary in 2.7% of patients in one case series[86] and accounted for 8% of all revisions in another[84]. Reasons for revision include the following:
        - Fracture: 7% of all revisions in one case series[84]
        - Discomfort: 1% of all revisions in one case series[84]
        - Insulation damage: 2.7% of patients in one case series[86]
        - One case series[89] reported wire extrusion through the skin at the receiver connector causing infection in 3% of patients, though details of the revision were not reported.
- Total removal (and replacement) of SCS system:
    - RCT: Removal and replacement of system due to local infection accounted for 3% of all revisions and 4% of patients[72].
    - RCT: Total removal of system due to recurrent rejection or relapsing ulcerative colitis ascribed to the SCS system accounted for 7% of all revisions and 8% of patients[72].
    - Total removal and replacement of the system was necessary in 1.2–6% of patients in four case series[85-88] and accounted for 17% of all revisions in another[84]. Reasons for removal (and replacement) include the following:
        - Infection: 3.0–6% of all patients in four case series[85-88]; accounted for 8% of removals from one case series[84] in which the systems were not replaced
        - New intolerable pain accounted for 8% of removals from one case series[84]; devices were not replaced

- No pain relief accounted for 1% of removals from one case series[84]; the system was not replaced
- A defective transmitter accounted for 1% of events from one case series[84]; the system was not replaced
- A MRI was necessary and accounted for 1% of events from one case series[84]; the system was not replaced

Table 7. Mid-term revision rates* (%) from one RCT and six case series

Author (Year)	Mean F/U (years) (range)	# patients with perm. SCS implants	Preoperative diagnosis (N, %)	Overall revision rate	Reason for revision
RCT					
Kemler (2008)	5.0 (no range)	N = 24 (20 available at f/u)	CRPS-I (100%)	42% (10/24) of patients (29‡ events) - - - - - - 54% (13/24) of patients had 17 pulse generator replacements	**Revision of electrode: 59% of events (17/29) (number of patients NR)** • repositioning of electrode (reason NR): 38% of events (11/29) • year 0–2: 8/11 • year 3: 0/11 • year 4: 1/11 • year 5: 2/11 • replacement of electrode (reason NR): 21% of events (6/29) • year 0–2: 2/6 • year 3: 1/6 • year 4: 2/6 • year 5: 1/6 **Revision of generator: 28% of events (8/29)** • painful pulse generator pocket: 28% of events (number of patients NR) • year 0–2: 7/8 • year 3: 1/8 • year 4: 0/8 • year 5: 0/8 **Revision of connecting cable/lead: NR** **Total removal and replacement of system: 3% of events (1/29) (4% of patients)** • infection (in year 0–2) **Total removal of system: 7% of events (2/29) (8% of patients)** • recurrent rejection: 3% of events (year 0–2) • relapsing ulcerative colitis caused by SCS system: 3% of events (year 0–2) - **Replacement of generator: 54% of patients (13/24) (17 procedures)** • 42 total pulse generators needed for 24 patients treated (mean battery life = 4 years)

Author (Year)	Mean F/U (years) (range)	# patients with perm. SCS implants	Preoperative diagnosis (N, %)	Overall revision rate	Reason for revision
					• year 0–2: 1/17 • year 3: 4/17 • year 4: 4/17 • year 5: 8/17
Case series					
Kay 2001[84]	5.2 (1–13)	N = 70	Neuropathic pain: 88% Ischemic pain: 5% Other/unknown: 6%	60% (42/70) of patients (72 events)	**Revision of electrode: 44% of revisions (32/72 events)** • inappropriate area of paraesthesia: 14% of all events • inadequate paraesthesia due to migration: 11% • inadequate paraesthesia due to fibrosis: 11% • inadequate paraesthesia – cause unknown: 7% • infection: 1% **Revision of generator: 30% of events (22/72 revisions)** • battery depletion: 22% of all events • mean battery life: 4.5 years (median 3.3 years) • discomfort/new pain: 6% • defective generator: 1% • displacement (pregnancy): 1% **Revision of connecting cable/lead: 8% of events (6/72 revisions)** • fracture: 7% of all events • discomfort/new pain: 1% **Total removal of system: 17% (12/72 events)** • new intolerable pain: 8% of events • pain from neurostimulation or laminotomy-related wound pain • infection: 4% • no pain relief: 1% • for MRI: 1% • defective transmitter: 1%
Kumar & Wilson 2007[86]	8.1 (range NR)	N = 338**	Neuropathic pain: 79.6% Ischemic pain: 15.7% Other: 4.8%	NR	**Revision of electrode: (summary rate NR)** • displaced electrode: 26.7% of patients • fractured electrode: 6.4% • hardware malfunction (increased impedance): 6.0% **Revision of generator: (summary rate NR)** • electrical leak: 1.2% of patients • displacement (due to improper placement): 1.2% • discomfort over pulse generator requiring repositioning: 1.5% **Revision of connecting cable/lead: (2.7% of patients)** • insulation damage: 2.7% **Total removal and replacement of system: (3.0% of patients)** • infection: 3.0%

Author (Year)	Mean F/U (years) (range)	# patients with perm. SCS implants	Preoperative diagnosis (N, %)	Overall revision rate	Reason for revision
Kumar & Toth 1998[85]	8.8 ± 4.5 (0.67–17)	N = 165	Neuropathic pain: 100%	NR	**Revision of electrode: (summary rate NR)** • displaced electrode: 33.5% of patients • fractured electrode: 3.6% • hardware malfunction: 3.6% **Revision of generator: (summary rate NR)** • electrical leak: 1.2% of patients **Total removal and replacement of system: (4.9% of patients)** • infection: 4.9%
Lanner 2007[87]	5.0 (1.25–6.25)	N = 88	Neuropathic pain: 98% Other: 2%	NR	**Revision of electrode: (summary rate NR)** • displaced electrode: "very few cases" **Revision of generator: (summary rate NR)** • dislocation: "very few cases" **Total removal and replacement of system: (6% of patients)** • infection: 6% of all patients
North 1993[88]	7.1 ± 4.5 (1.5–20.4)	N = 249††	Neuropathic pain: 100%††	NR	**Revision of electrode: (7.4% of all systems)** • electromechanical failure: 7.4% of all systems (22/298 systems implanted in 249 patients) **Revision of generator: (5.4% of all systems)** • generator failure: 5.4% of systems (16/298) **Total removal and replacement of system: (5.3% of patients)** • infection: 5.3% of all patients (9/171)
Sanchez-Ledesma 1989[89]	5.5 (range NR)	N = 36	Neuropathic pain: 100%‡‡	NR	**Revision of electrode: (3% of patients)** • dislodgement of electrode: 3% of all patients **Revision (component NR): (3% of patients)** • wire extrusion through skin at the receiver connector; infection: 3% of all patients

***** Additional details can be found in Supplemental Table 5 (demographic information) and Supplemental Table 6 (safety data).

† Kemler 2008: safety data reported on all patients randomized to receive SCS that underwent permanent implants; 20/24 patients were available for 5-year follow-up.

‡ Not including pulse generator replacements. Of the 29 total revisions, 72% (21/29) occurred the first two years, 7% (2/29) occurred in year 3, 10% (3/29) occurred in year 4, and 10% (3/29) occurred in year 5.

** Kumar & Wilson 2007: 336/338 patients available for follow-up and used to calculate complication rates.

†† North 1993: 171/249 patients available for follow-up; demographic information includes only the 171/249 patients available at follow-up.

‡‡ Sanchez-Ledesma 1989: demographic information includes all patients enrolled, only 36/49 underwent permanent SCS device implantation.

4.2.2. Other SCS related complications

Short-term follow-up: comparative studies

Complications or side effects ascribed to the SCS device were reported by two RCTs and one cohort study; overall rates ranged from 8–100% of patients. At 24 months follow-up, Kemler et al. noted that side effects had occurred in 100% of the patients available for the 24-month follow-up with implanted systems[71]; it is likely that these side effects may have led to revision in some cases, but the data could not be separated out. The authors of the PROCESS trial[13, 74] reported device-related complications not requiring revision in 14% of patients by two years after implantation. The rates of each of these complications could not be separated out from those requiring revision. Details can be found in Supplemental Table 4. Complications included:

- Dural puncture (4–8% of patients), with associated headache in some patients [25, 75]; one of these patients had implantation terminated as a result[75]
- Change in amplitude by bodily movements: 86% of patients[71]
- Paresthesia in other body parts: 50% of patients[71]
- Pain or irritation from pulse generator: 45% of patients[71]
- More pain in other body parts: 32% of patients[71]
- Disturbed urination: 18% of patients[71]
- Movements or cramps resulting from elevated amplitude: 14% of patients[71]
- Lead/extension fracture/torqued contacts: 5% of patients[74]
- Loss of therapeutic effect, loss of paresthesia, or unpleasant paresthesia: 7% of patients[74]
- Infection: 5–11% of patients[74, 75]
- Pain at generator incision site: 10% of patients[74]
- Fluid collection at neurostimulator pocket: 5% of patients[74]
- Pain over SCS components: 18% of patients[75]

In addition, one cohort study[75] reported complications associated with trial stimulation in 16% of patients:

- Symptoms of unknown etiology: 10% of patients[75]
- Fluid leaking at electrode site: 2% of patients[75]
- Severe post-spinal headache: 2% of patients[75]
- Extensive epidural abscess requiring irrigation, debridement, and a T2–L3 hemilaminotomy; one day following this surgery the patient underwent respiratory arrest, nearly died, and required mechanical ventilation: 2% of patients[75]

Mid-term follow-up: comparative studies and case series

In their RCT, Kemler et al. (2008)[72] did not report any device-related complications or side effects by five years[71].

Complications related to the SCS device (which may have necessitated reoperation) were reported all six case series[84-89] and included the following (summary rates were not reported):

- Infection, including wound infections and epidural abscesses: 0– 6% of patients as reported by all six case series[84-89]
- Discomfort over pulse generator: 6.5% of patients as reported by one case series[86]
- Subcutaneous hematoma: 5.7% of patients as reported by one case series[86]
- Cerebrospinal fluid leak: 0.6% of patients as reported by two case series[85, 86]

4.2.3. Non-SCS related complications

Short-term follow-up: comparative studies

One RCT reported complications unrelated to the SCS device in 35% of patients randomized to receive SCS + CMM (18/52) (25 events) and in 52% of patients randomized to receive CMM (25/48) (37 events) at one-year follow-up[13]. At two years follow-up, 31% of patients in the SCS group (13/42) had experienced a total of 15 complications unrelated to the device; this data was not reported for the CMM group[74]. Complications include the following:

- New illness, injury, or condition:
  - SCS + CMM group: 25% and 17% of patients (1 and 2 years f/u, respectively)[13, 74]
  - CMM group: 23% of patients (1 year f/u)[13]
- Worsening of the pre-existing condition:
  - SCS group: 13% and 17% of patients (1 and 2 years f/u, respectively)[13, 74]
  - CMM group: 15% of patients (1 year f/u)[13]
- Drug adverse events:
  - SCS + CMM group: 4% of patients (1 year f/u)[13]
  - CMM group: 21% of patients (1 year f/u)[13]
- Extra pain events:
  - SCS + CMM group: 0% of patients (1 year f/u)[13]
  - CMM group: 23% of patients (1 year f/u)[13]

Two RCTs[14, 25, 71] did not report on any complications unrelated to the device for either the SCS or comparative groups (physical therapy, reoperation).

Mid-term follow-up: comparative studies and case series

The RCT[72] did not report any complications unrelated to the device for either the SCS or physical therapy groups.

Complications unrelated to the SCS were not reported by any of the case series.

4.2.4. Mortality

Three RCTs and one cohort study reported short-term mortality rates[13, 14, 71, 74, 75]. All studies reported at least two years follow-up. There were 2 deaths in the SCS groups (patients may or may not have had a permanent device implanted), 2/139; one death occurring at six months due to a sudden "cardiac events" that was not attributed to SCS[14] and one death occurring between six and twelve months (cause not reported)[75]. The control groups reported no deaths during the same time period (0/179)[13, 14, 25, 71, 74, 75].

One RCT reported mid-term mortality. At 5.0 years, the mortality rate was 0% for both the SCS (0/31) and physical therapy (0/13) groups[72]. Mortality was documented in three case series[84, 87, 89] with mid-term follow-up. There were 2 deaths in 194 patients receiving SCS implants (no control groups for comparison). Death was caused by cerebrovascular accident in one patient (who successfully received SCS for angina, not neuropathic pain), and suicide in the second patient[84].

In no case was the cause of death attributed to the SCS device or procedure for implanting or revising the device. It should be noted that in general, mortality is not discussed in the studies we identified as an SCS-related adverse event. However, one cohort study[75] reported that a patient nearly died as a result of trial stimulation. The patient experienced an epidural abscess requiring irrigation, debridement, and a T2–L3 hemilaminotomy; one day following this surgery the patient underwent respiratory arrest and nearly died. Mechanical ventilation was required.

We identified an additional study by Coffey et al (2009)[90] that compared mortality from all causes (including ischemic and neuropathic) among patients receiving intrathecal opioid pumps with those receiving SCS implantation (control group). This study did not meet our criteria for inclusion and is discussed in Appendix F.

4.2.5. Manufacturer and User Facility Device Experience (MAUDE)

The FDA's MAUDE database of adverse events (updated on June 30, 2010) was searched. Approximately 1400 adverse event reports have been made related to SCS from August 1, 1996 to June 30, 2010. Report initiators include manufacturers, clinical users/providers, attorneys and patients. It is unclear how many are unique reports. Some provide information regarding the severity, type and resolution of adverse events while others do not. Summary and categorization of these is beyond the scope of this report and since no denominator information is available to provide rate information, it is not possible to put these reports into a meaningful context.

Summary for Key question 2:
What is the evidence of safety of spinal cord stimulation?

Short-term (< 5 years) safety data were reported by three RCTs and one prospective cohort study; mid-term (5–10 years) safety data were reported by one RCT and six case series. No long-term safety data were available.

Revision
All three RCTs and the one cohort study reported short-term revision rates of SCS devices; one RCT and all six case series reported mid-term revision rates. However, each study reported the data differently, and not all studies reported an overall revision rate (the proportion of patients with one or more revision). Therefore, revision rates were difficult to pool. Reasons for revision included (but were not limited to): revision or replacement of electrodes/leads due to migration, improvement of paresthesia, defective electrodes, infection, fractured electrode, or hardware malfunction; revision or replacement of generators (or stimulators) due to painful pulse generator pockets, migration, battery depletion, defective generator, electrical leak, or failure; revision of the connecting cable/lead due to fracture, discomfort, or insulation damage; SCS systems were explanted (and often reimplanted) due to infection, recurrent rejection, discomfort, ineffective pain relief, new intolerable pain, defective transmitters, or seizures.

Other SCS-related complications or side effects
Complications or side effects ascribed to the SCS device were reported by two RCTs, one cohort study, and six case series; overall short-term rates ranged from 8–100% of patients. At two years follow-up, one RCT reported that side effects had occurred in 100% of available SCS patient; another RCT reported device-related complications not requiring revision in 14% of patients. Complications or side effects ascribed to the SCS system included: change in amplitude by bodily movements, paresthesia in other body parts, pain or irritation from pulse generator, disturbed urination, movements or cramps resulting from elevated amplitute, infection, loss of therapeutic effect, loss of parasthesia, or unpleasant paresthesia, subcutaneous hematoma, cerebrospinal fluid leak, dural puncture, or pain over SCS components.

Complications not related to SCS
Complications not related to SCS were reported by one RCT. Rates of new illness, injury, or condition and of worsening of the pre-existing condition were similar for both the SCS and the CMM group; however the percentage of patients that had experienced drug adverse events or extra pain events were 15 to 23% higher in the CMM group than in the SCS group at one year.

Mortality
Short-term mortality data were obtained from three RCTs and one prospective cohort study. Two deaths occurred in the SCS groups (2/139); one due to a sudden cardiac event at six months and another between six and twelve months for which the cause was not reported. No deaths occurred in any of the control groups (0/179). Mid-term mortality data were obtained from one RCT and three case-series. Two deaths occurred in SCS patients; one due to cerebrovascular accident in a patient being treated for angina, not neuropathic pain, and another due to suicide. No deaths were attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.

4.3. Key Question 3: Is there evidence of differential efficacy or safety issues in subpopulations with use spinal cord stimulation?

We identified six prognostic studies with Level of Evidence (LoE) grades of I or II: three were prospective and two were retrospective studies; one had an LoE grade of I, while the other five received an LoE grade of II. Patient diagnoses varied by study, but 100% of patients had some form of neuropathic pain (see Supplemental Table 7 for more details). Most of the data from these studies were fairly limited, as authors tended towards reporting only p-values but not outcome data. In general, the studies were small, with permanent SCS devices implanted in 32 to 53 patients (range). The studies were likely underpowered, and larger studies are needed to more effectively determine whether any prognostic factors are associated with improved outcomes following SCS.

Outcomes from the prognostic cohort studies are summarized below and in Table 8.

Age

Three studies evaluated whether age had an effect on pain relief experienced in the first year (range, 0.25–1.0 year) following SCS. These studies were all small, with a mean patient number of 34 (range, N = 32–36). One study[91] found that younger age was significantly correlated with pain relief of at least 50% (at three months compared to baseline) by univariate (P = .004) analysis. No details regarding the age threshold were provided. Multivariate analysis was performed to generate a prediction equation, which showed that the percent change in VAS scores was significantly associated with patient age, the depression scale of the MMPI (D), and the evaluative subscale of the McGill Pain Questionnaire (MPQe): $\%\Delta VAS = 112.57 - 1.98(D) - 1.68(age) + 35.54(MPQe)$. The two other cohort studies[61, 92] found no association between patient age and pain relief.

One prospective cohort study[61] (N = 32) further demonstrated that age was not correlated with SF-36 or GPE scores at nine months.

Sex

Four cohort studies evaluated the effect of patient sex on pain relief following SCS. Three studies[61, 91, 92] found that sex was not predictive of pain relief in the first year (range, 0.25–1.0 years) following device implantation; one study[61] found no correlation between patient sex and SF-36 or GPE scores at nine months.

In contrast, one retrospective cohort study[93] on FBSS patients showed that the success rate at 5 years was significantly higher in females by both univariate (P = .003) and multivariate (P < .05) analyses. Success was defined as pain relief of at least 50% and patient satisfaction. This study also found that females had significant improvements in a combination of everyday activities (ability to work, walk, climb stairs, sleep, have sex, drive, and eat), neurological function (strength, sensation, and bladder/bowel control), and medication use by multivariate analysis (P = .009).

Workers' compensation or other disability payments

One study[91] found no difference in the percentage of patients receiving workers' compensation or other disability payments than those not under such programs who achieved at least 50% pain relief at three months (compared with baseline).

Another prospective study (Turner (2010))[75] found that among patients on workers' compensation, a successful composite outcome 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.

Characteristics of pain

Lamé et al. (2009) found that CRPS-I patients with a longer duration of chronic pain had significant improvements in quality of life at nine months as measured by two domains of the SF-36 outcome measure by multivariate analysis (social functioning, P = .03; bodily pain, P = .01). Duration of chronic pain was not associated with improvements in the six other domains of the SF-36, nor was it correlated with significant improvements in global perceived effect (GPE) scores or pain relief.

Two other cohort studies[91, 92] reported no association between pain duration and pain relief at three and twelve months.

One retrospective study[92] found no association between the pain intensity at baseline (VAS ≥ 7.1 versus < 7.1) and pain relief at one year (P = .20).

Four studies[61, 91-93] found no significant correlation between pain location (which varied by study) and pain relief at follow-up, which ranged from three months to five years. One study found no difference in nine-month SF-36 and GPE scores between patients with hand pain and those with foot pain; another study[93] found no difference in a combination of everyday activities, neurological function, and medication use between FBSS patients with primarily axial versus those with primarily radicular pain.

One study[75] on workers' compensation FBSS patients found that at 12 months, a higher percentage of SCS patients with unilateral pain achieved leg pain relief of at least 50% compared with SCS patients with bilateral pain (21% versus 9%, respectively; *P* = not reported); similarly, more patients with unilateral pain had functional improvement (as measured by ≥ 2 point increase in RDQ scores from baseline) compared with those patients with bilateral pain (46% versus 17%, respectively; *P* = not reported).

The predictive effect of baseline McGill Pain Questionnaire scores was evaluated in two cohort studies. Although Burchiel et al. (1995)[91] found no significant association with any component of the outcome measure with pain relief at three months by univariate analysis, they reported that the evaluative scale score was significantly associated with age and the depression subscale score of the MMPI in the percent change in VAS score at three months: $\%\Delta VAS = 112.57 - 1.98(D) - 1.68(age) + 35.54(MPQe)$. Thus, higher McGill evaluative subscores, lower patient age, and

lower depression subscale scores were associated with improved pain relief. One additional study[93] reported that none of the domains of the McGill Pain Questionnaire were predictive of success (pain relief of at least 50% and patient satisfaction) at five years.

One recent retrospective study[92] on the 36 CRPS-I patients enrolled in the Kemler RCT[25] and randomized to receive SCS demonstrated that the absence of brush-evoked allodynia at baseline was significantly correlated with success at one-year follow-up (absent: 81% success rate, moderate: 50%, and severe: 31%; P = .017). "Success" was defined as a reduction in VAS scores by at least 2.5 cm and/or a patients global impression of change (PGIC) score of "much improved" or "very much improved". In contrast, the presence of mechanical hypoesthesia at baseline was not correlated with success.

Prior operations for chronic pain

The time since the first lumbar surgery was not predictive of success (pain relief ≥ 50% and patient satisfactions) at five years in a small population of FBSS patients from one retrospective study[93]. This study also found no correlation between the time elapsed since the first operation or the number of prior operations for pain with a combined outcome score for everyday activities, neurological function, and medication use.

Two studies showed no relationship between the number of previous operations for chronic pain and pain relief at three months[91] or success (as defined above) at five years[93].

Psychological status

The psychological status of patients was evaluated at baseline in three studies with five different outcome measures (Minnesota Multiphasic Personality Inventory (MMPI), SF-36 Mental Health Component, Beck Depression Inventory, Symptom Checklist-90, and Derogatis Affects Balance Scale (DABS)). Only the depression (D) domain of the MMPI correlated with pain relief of at least 50% at three months follow-up in one study[91]; none of the other domains or the Beck Depression Inventory were predictive of pain relief in this study. Similarly, the other study[94] reported that the scores of the Symptom Checklist-90 and DABS questionnaires at baseline were not significantly associated with pain relief at a mean of 3.5 years follow-up (range, 2 to 13.5 years).

One study[75] on workers' compensation patients found that more SCS patients who had SF-36 Mental Health scores in the highest third SF-36 at baseline achieved 50% or more reduction in leg pain at 12 months compared with those patients who scored in the lowest third (29% versus 11%, respectively; *P* = not reported). Similar results were found when evaluating for the percentage of patients who achieved at least a 2-point increase in their RDQ score at 12 months compared to baseline (57% versus 16%, respectively; *P* = not reported).

Although Medicare and other private third-party insurers require psychological screening prior to SCS implantation, these results are conflicting whether patient scat baseline may not in concordance with those of a systematic review which reported

Table 8. Prognostic factors for SCS evaluated in six cohort studies.

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
Age	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .004 ◆ favoring younger pts (details NR) ◆ data NR Multivariate: ◆ *P* = .0002 ◆ favoring younger pts (details NR) ◆ (see predictive equation, text)	---	---	---
	Lamé (2009)	Prospec.	N = 32	0.75 (no range)	Mean age ± SD: ◆ pain relief ≥ 50%: 40.5 ± 9.9 years ◆ pain relief < 50%: 38.2 ± 10.6 years ◆ *P* = .54 (NS)	Multivariate (*post-hoc)*: ◆ *P* = NS for all domains ◆ data NR	Mean age ± SD: ◆ GPE score 6–7: 40.8 ± 9.8 years ◆ GPE score ≤ 5: 37.1 ± 10.7 years ◆ *P* = .32 (NS)	---
	Van Eijs (2010)	Retro.	N = 36‡	1.0 (no range)	Success**: ◆ Age ≤ 40 years: 65% ◆ Age > 40 years: 44% ◆ *P* = .20 (NS)	---	---	---
Sex	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .3 (NS) ◆ (details NR) - - - - - - - - - - - - ***% pain relief:*** ◆ females: 56% pain relief ◆ males: 34% pain relief	---	---	---

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
					◆ *P* = .06 (NS) ***Change in VAS score:*** ◆ *P* = .1 (NS) ◆ data NR			
	Lamé (2009)	Prospec.	N = 32	0.75 (no range)	Pain relief ≥ 50%: ◆ females: 40% ◆ males: 29% ◆ *P* = .68 (NS)	Multivariate (*post-hoc)*: ◆ *P* = NS for all domains ◆ data NR	GPE score ≥6: ◆ females: 52% ◆ males: 57% ◆ *P* = 1.00 (NS)	---
	North (1991)	Retro.	N = 53	5.0 (no range)	Success (≥ 50% pain relief and patient satisfaction): ◆ *P* = .003 (favoring females) (univariate analysis) ◆ *P* < .05 (favoring females) (multivariate analysis) ◆ data NR	---	---	*Function/ Activity/ Med use** ◆ *P* = .009 (favoring females) (multi-variate analysis) ◆ data NR
	Van Eijs (2010)	Retro.	N = 36‡	1.0 (no range)	Success**: ◆ female: 64% ◆ male: 43% ◆ *P* = .22 (NS)	---	---	---
Workers' compensation or other disability payments	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .5 (NS) ◆ data NR ◆ details NR	---	---	---
Pain intensity	Van Eijs	Retro.	N = 36‡	1.0	Success**:	---	---	---

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
(baseline)	(2010)			(no range)	◆ VAS ≤ 7.1: 57% ◆ VAS > 7.1: 53% ◆ *P* = .20 (NS)			
Duration of pain	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .6 (NS) ◆ details NR ◆ data NR	---	---	---
	Lamé (2009)	Prospec.	N = 32	0.75 (no range)	Mean duration ± SD: ◆ pain relief ≥ 50%: 5.3 ± 4.6 years ◆ pain relief < 50%: 4.0 ± 2.2 ◆ *P* = .29 (NS) (univariate analysis) ◆ *P* = NS (multivariate analysis)	Multivariate (*post-hoc)*: ◆ Social function-ing: *P* = .03 ◆ Bodily pain: *P* = .01 ◆ *P* = NS for all other domains ◆ data NR	Mean duration ± SD: ◆ GPE score 6–7: 5.4 ± 4.0 years ◆ GPE score ≤ 5: 3.5 ± 2.0 years ◆ *P* = .09 (NS) (univariate analysis) ◆ *P* = NS (multi-variate analysis)	---
	Van Eijs (2010)	Retro.	N = 36‡	1.0 (no range)	Success**: ◆ Pain < 40 months: 62% ◆ Pain ≥ 40 months: 47% ◆ *P* = .36 (NS)	---	---	---
Time since first lumbar surgery	North (1991)	Retro.	N = 53	5.0 (no range)	Success (≥ 50% pain relief and patient satisfaction): ◆ *P* = NS ◆ data NR	---	---	*Function/ Activity/ Med use** ◆ *P* = NS ◆ data NR
Number of prior operations for	Burchiel (1995)	Prospec.	N = 34†	0.25 (no	Univariate: ◆ *P* = .1 (NS)	---	---	---

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
pain				range)	◆ details NR ◆ data NR			
	North (1991)	Retro.	N = 53	5.0 (no range)	Success (≥ 50% pain relief and patient satisfaction): ◆ *P* = NS ◆ data NR	---	---	*Function/ Activity/ Med use** ◆ *P* = NS ◆ data NR
Pain location	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .2 (NS) ◆ Back & legs versus legs only ◆ data NR	---	---	---
	Lamé (2009)	Prospec.	N = 32	0.75 (no range)	Pain relief ≥ 50%: ◆ Hand: 40% ◆ Foot: 35% ◆ *P* = 1.00 (NS)	Multivariate (*post-hoc)*: ◆ *P* = NS for all domains ◆ data NR	GPE score ≥6: ◆ Hand: 60% ◆ Foot: 47% ◆ *P* = .50 (NS)	---
	North (1991)	Retro.	N = 53	5.0 (no range)	Success (≥ 50% pain relief and patient satisfaction): ◆ *P* = NS (axial vs radicular pain) ◆ data NR	---	---	*Function/ Activity/ Med use** ◆ *P* = NS (axial vs radicular pain) ◆ data NR
	Van Eijs (2010)	Retro.	N = 36‡	1.0 (no range)	Success**: ◆ upper limb: 55% ◆ lower limb: 57% ◆ *P* = .88 (NS)	---	---	---
Laterality of pain	Turner (2010)	Prospec.	SCS: N = 51 PC: N = 39	1.0 (no range)	<u>SCS:</u> • Unilateral, leg pain relief ≥ 50%: 21% • Bilateral, leg	---	---	*RDQ improvement ≥ 2 points:* <u>SCS:</u> • Unilateral,

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
			UC: N = 68		pain relief ≥ 50%: 9% • *P* = NR			RDQ ≥ 2 pts: 46% • Bilateral, RDQ ≥ 2 pts: 17% • *P* = NR
Pain catastrophizing score	Lamé (2009)	Prospec.	N = 32	0.75 (no range)	Mean PCS ± SD: ◆ pain relief ≥ 50%: 34.4 ± 4.9 ◆ pain relief < 50%: 29.0 ± 12.0 ◆ *P* = .15 (NS) (univariate analysis) ◆ *P* = NS (multivariate analysis)	Multivariate (*post-hoc)*: ◆ *P* = NS for all domains ◆ data NR	Mean PCS ± SD: ◆ GPE score 6–7: 30.1 ± 10.4 ◆ GPE score ≤ 5: 32.1 ± 10.2 ◆ *P* = .59 (NS) (univariate analysis) ◆ *P* = NS (multi-variate analysis)	---
Presence of allodynia (baseline)	Van Eijs (2010)	Retro.	N = 36‡	1.0 (no range)	Success**: ◆ absent: 81% ◆ moderate: 50% ◆ severe: 31% ◆ *P* = .017 (univariate) ◆ Multivariate analysis used to estimate cutoff point for pain intensity (see text)	---	---	---
Presence of hypoesthesia (baseline)	Van Eijs (2010)	Retro.	N = 36‡	1.0 (no range)	Success**: ◆ Absent/light: 59% ◆ severe: 60% ◆ *P* = .55 (NS)	---	---	---

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
Education	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .3 (NS) ◆ details NR ◆ data NR	---	---	---
	Lamé (2009)	Prospec.	N = 32	0.75 (no range)	Pain relief ≥ 50%: ◆ High (secondary) education: 24% ◆ Low (vocational) education: 53% ◆ *P* = .14 (NS)	Multivariate (*post-hoc)*: ◆ General health: *P* = .04 (favoring high (second-ary) education ◆ *P* = NS for all other domains ◆ data NR	GPE score ≥6: ◆ High (secondary) education: 53% ◆ Low (vocational) education: 53% ◆ *P* = 1.00 (NS)	---
McGill Pain Questionnaire	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = NS for all 4 sections Multivariate: ◆ Evaluative scale: *P* = .002 (favoring higher scores) (see predictive equation, text) ◆ *P* = NS for remaining 3 scales	---	---	---
	North (1991)	Retro.	N = 53	5.0 (no range)	Success (≥ 50% pain relief and patient satisfaction): ◆ *P* = NS for all domains and choice of	---	---	---

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
					adjectives (univariate (and for some, multivariate) analysis)			
MMPI	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ Depression (D), age: *P* = .006 ◆ *P* = NS for all other 9 scales Multivariate: ◆ Depression (D): *P* = .002 (favoring lower scores) (see predictive equation, text)	---	---	---
	North (1996)	Prospec.	N = 35	3.5 (2–13.5)	Univariate: ◆ *P* = NS for all scales Multivariate: ◆ *P* = NS for all scales	---	---	---
SF-36 Mental Health Component	Turner (2010)	Prospec.	SCS: N = 51 PC: N = 39 UC: N = 68	1.0 (no range)	SCS: • "highest††", leg pain relief ≥ 50%: 29% • "lowest††", leg pain relief ≥ 50%: 11% • *P* = NR	---	---	*RDQ improvement ≥ 2 points* SCS: • "highest††", RDQ ≥ 2 pts: 57% • "lowest††", RDQ ≥ 2 pts: 16% • *P* = NR
ODI	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .1 (NS) ◆ data NR	---	---	---

Prognostic factor	Author	Study design	Patient number	Mean F/U yrs (range)	Outcomes			
					Pain relief ≥ 50%	SF-36 score	GPE score	Function
Beck Depression Inventory	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = .5 (NS) ◆ data NR	---	---	---
Sickness Impact Profile	Burchiel (1995)	Prospec.	N = 34†	0.25 (no range)	Univariate: ◆ *P* = NS for all 4 sections	---	---	---
Symptom Check List-90 (revised)	North (1996)	Prospec.	N = 35	3.5 (2–13.5)	Univariate: ◆ *P* = NS for all scales Multivariate: ◆ *P* = NS for all scales	---	---	---
DABS	North (1996)	Prospec.	N = 35	3.5 (2–13.5)	Univariate: ◆ *P* = NS for all scales Multivariate: ◆ *P* = NS for all scales	---	---	---

DABS: Derogatis Affects Balance Scale
MMPI: Minnesota Multiphasic Personality Inventory
NR: not reported
NS: not statistically significant
ODI: Oswestry Disability Index
PC: pain clinic
PGIC: patients global impression of change
Prospec.: prospective cohort study
RDQ: Roland-Morris Disability Questionnaire
Retro.: retrospective cohort study
SD: standard deviation
UC: usual care
* Combination of everyday activities, medication usage, and neurological function
† Burchiel: original patient number was N = 40. Three patients were excluded by imposing the following constraints: (1) if there was at least at 50% improvement in VAS scores from baseline, the overall patient description of pain relief needed to be "excellent" (n = 1 excluded); (2) if there was less than 50% improvement in VAS scores from baseline, the overall patient description of pain relief needed to be "fair, good, or excellent" (n = 1 excluded); (3) the patient's description of the location of pain needed to be consistent (n = 1 excluded). An additional three patients were excluded due to incomplete data sets.
‡ Van Eijs: the analyses were based on 36 patients from the Kemler RCT[25] who underwent trial stimulation; however only 24/36 patients received permanent implants.
** Van Eijs: "success": patients with SCS were considered successful at the 12-month f/u if they had sustained pain reduction, as defined by a reduction in their VAS by ≥ 2.5 and/or a PGIC score of "much improved" or "very much improved" at 3 of the 4 follow-up visits.
†† Turner 2010: "highest" – patients with SF-36 Mental Health scores in the highest third; "lowest" – patients with SF-36 Mental Health scores in the lowest third

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

We identified five small prognostic studies (three prospective and two retrospective studies). In general, very little evidence was found that suggests that any of the factors evaluated were associated with improved outcome following SCS. Prognostic factors evaluated included:

Age
Three studies evaluated whether age had an effect on pain relief in the first year following implantation. While one study reported that younger age was significantly associated with improved pain relief, two other studies found no association between patient age and pain relief. Furthermore, one prospective cohort study demonstrated that age was not correlated with SF-36 or GPE scores at nine months

Sex
Four studies evaluated the effect of patient sex on pain relief following SCS. Three studies found that sex was not predictive of pain relief in the first year, and one study reported that success at five years was significantly higher in females. This study also reported that females had significant improvements in a combination of everyday activities (ability to work, walk, climb stairs, sleep, have sex, drive, and eat), neurological function (strength, sensation, and bladder/bowel control), and medication use. One other study found no correlation between patient sex and SF-36 or GPE scores at nine months.

Workers' compensation or other disability payments
One study found no difference in the percentage of patients who achieved at least 50% pain relief at three months between those receiving workers' compensation or other disability payments than those not under such programs.

Duration of pain
Two studies evaluated and found no relationship between duration of chronic pain and pain relief in the first year following SCS implantation. One study reported that CRPS patients with a longer duration of chronic pain had significant improvements in quality of life at nine months as measured by two (of eight) domains of the SF-36 outcome measure by multivariate analysis; however, no association was found between pain duration and GPE scores.

Pain intensity
One study evaluated and found no association between the pain intensity at baseline and pain relief at one year.

Time since first lumbar surgery
One study found that the time since the first lumbar surgery was not associated with success or a composite score that included everyday activities, neurological function, and medication use at five years.

Number of prior operations for pain
Two studies evaluated and found no association between the number of previous operations for chronic pain and pain relief at three months or success at five years.

Pain location
Four studies evaluated and found no association between pain location and pain relief at follow-up, though each study compared different locations. One study reported no association between hand versus foot pain with nine-month SF-36 or GPE scores; another study found no difference in a combination of everyday activities, neurological function, and medication use between patients with axial versus radicular pain.

Laterality of pain
One study suggested that more SCS patients with unilateral pain achieved leg pain relief of at least 50% than did those patients with bilateral pain; similarly, more patients with unilateral pain had functional improvement (as measured by the RDQ) compared with those patients with bilateral pain.

Allodynia or hyposthesia at baseline
One retrospective study demonstrated that the absence of brush-evoked allodynia at baseline was significantly associated with success at one-year. In contrast, the presence of mechanical hypoesthesia at baseline was not correlated with success.

McGill Pain Questionnaire
Two studies evaluated the predictive effect of baseline McGill Pain Questionnaire scores with conflicting results. While one study found that higher McGill evaluative subscores were associated with improved pain relief, the other study found that none of the domains of the McGill Pain Questionnaire were predictive of success at five years.

Minnesota Multiphasic Personality Inventory (MMPI)
Two studies evaluated whether MMPI scores at baseline were associated with improved pain relief. One study found that lower scores for the depression subscale were significantly correlated with pain relief at three months, while the other study found no correlation between MMPI scores and pain relief at a mean of 3.5 years.

SF-36 Mental Health Component
One study found that SCS patients with baseline SF-36 Mental Health scores in the top third of patients had better pain relief and functional outcomes (as measured by the RDQ) compared with those patients with baseline scores in the lowest third.

4.4. What is the evidence of cost effectiveness of spinal cord stimulation?

Three complete economic evaluations in the peer-reviewed medical literature met inclusion criteria for this review. Two were published economic evaluations of SCS compared with other interventions for pain and one was included as part of the recent HTA conducted by NICE in the UK. Since all three studies included cost-utility analysis, which allows for comparison across studies, this is the focus in this section. Difference in interventions evaluated in these studies needs to be considered, however. Summaries of the economic studies are presented in Table 9.

Taylor and Taylor 2005[95]

Taylor and Taylor (2005)[95] conducted cost-utility analyses to estimate both the short- and long-term value of spinal cord stimulation compared with conventional medical management (CMM) in patients with FBSS. For the short-term analysis, the authors estimated costs and effects for two years using a decision tree model based on a previously published disease model[96]. Short-term SCS data were obtained from one published randomized controlled trial with a mean follow-up of 2.9 years (North 2005)[14], and indirect comparison CMM data were obtained from a second RCT that evaluated outcomes two years following CMM versus reoperation in patients with chronic leg and back pain[97]. Four possible health states were possible at two years and included satisfactory or unsatisfactory pain relief, with or without complications; however, because the RCT[97] reported a two-year complication rate of 0% in CMM patients, the authors assumed that CMM patients do not undergo complications. To estimate lifetime cost-utility, Taylor and Taylor built a Markov model that extended these results to estimate costs and outcomes in four-year cycles for the life expectancy of each patient. At the end of each cycle, patients were considered to have satisfactory or unsatisfactory pain relief with or without complications (CMM patients again were assumed to have no complications), and accrued an associated cost and utility for that outcome. Data sources for the Markov model were published observational studies.

The study results suggested that at two years, SCS would achieve both improved utility (based on pain relief and complications) and higher costs, at an incremental cost-effectiveness ratio of €45,819 per QALY gained. On one-way sensitivity analysis, in which one parameter at a time is varied to see the effect on the final result, the model was most sensitive to SCS effectiveness and complication rates. In the lifetime analysis, SCS was considered to dominate CMM, thus SCS achieved both improved utility (+ 1.12 QALYs per patient) and lower costs compared with CMM. This finding remained at all levels of sensitivity analysis.

Overall, this is a well-conducted economic evaluation. The model inputs and structure are clearly presented; data from RCTs is used where possible; and a long-term time horizon is adopted. The choice of comparator (CMM) simulates clinical care and includes appropriate model inputs and costs.

North 2007[98]

North et al. (2007)[98] performed a cost utility study alongside the North (2005)[14] RCT, which was conducted at a single US center and compared SCS to reoperation in FBSS patients (crossover allowed after six months). Clinical, hospital charge, and cost data were available at a mean of 3.1 (range, 1.6–4.7) years from 40 of the first 42 consecutive patients. The authors performed both cost-effectiveness (cost per success, defined as pain relief ≥ 50% and patient satisfaction) and cost-utility analyses under the three conditions of the trial (intent-to-treat, treated as randomized (with crossovers considered failures), and per-protocol) and conducted probabilistic sensitivity analysis using bootstrap methods.

In none of the analyses was the difference in mean QALY between the SCS and reoperation groups statistically significant. However, in all three analyses and on sensitivity analysis, SCS was dominant over reoperation in both the incremental cost effectiveness ratio (ICER) (cost/success) and in the incremental cost utility ratio (ICUR) (cost per QALY); thus SCS was associated with improved outcomes and lower costs compared with reoperation (Table 9).

This study was the only one we reviewed that was conducted in the US, which may improve the generalizability of the findings to a US policy environment; however, the small patient population and sole use of hospital charge data provide a relatively limited perspective. In addition, this was the only study that used reoperation as the comparator rather than CMM, whose costs are likely lower in the short term. The authors acknowledged that the study was likely underpowered and disclosed that the study was funded by Medtronic. Overall, this study has limited usefulness to decision-makers but provides the only data on the use and hospital charges associated with SCS and reoperation in a US setting that we are aware of.

Simpson 2009[36]

As part of the recent NICE HTA (2009)[36], the economic evaluation considered three approaches: (1) a systematic literature review of economic studies conducted in the UK; (2) an economic model submitted by the Association of British Healthcare Industries (ABHI) on behalf of several manufacturers (Advanced Neuromodulation Systems (St. Jude Medical), Boston Scientific, and Medtronic); and (3) an independently conducted economic evaluation (from the School of Health and Related Research (ScHARR) at The University of Sheffield).

For the systematic literature review, the authors identified one study for inclusion, Taylor and Taylor 2005[95], which we also included and is reviewed above.

The two economic models were both judged by the authors to be of appropriate quality and scope. Both evaluations used data from the three RCTs[13, 14, 25] reviewed in this HTA. Cost per QALY was determined for three comparisons: SCS plus CMM versus CMM alone in CRPS patients[25], SCS plus CMM versus CMM alone in FBSS patients[13], and SCS plus CMM versus reoperation in FBSS patients[14]. Both models considered pain relief of at least 50% as treatment success. Both used a decision analytic model to estimate outcomes to six months and Markov modeling to estimate costs and outcomes to 15 years, and both used probabilistic methods for sensitivity analysis, and provide results in the form of a base case analysis (four years) and device cost (at varying time points).

In both the manufacturer's and the ScHARR evaluations for each of the three analyses, SCS plus CMM was found to be dominant over its comparator. In the CRPS model, SCS plus CMM was associated with improved outcomes and increased costs in the short-term than CMM alone, except the base case incremental cost effectiveness ratio (ICER) was higher than in the FBSS model. The higher ICER in the CRPS models may be due to smaller differences in QALYs between intervention and comparator than in the FBSS models (Table 9).

For FBSS, SCS plus CMM was associated with improved outcomes and increased costs in the short-term versus both comparators, at cost-effectiveness ratios normally considered acceptable by the NHS (roughly £20,000/QALY). Cost-effectiveness ratios decreased over time, until SCS + CMM dominated each comparator after seven years.

The Simpson 2009 appraisal of the manufacture's and the ScHARR's evaluation was thorough and of high quality; however, its results may not be completely transferable to the US setting given the differences in health care systems and reimbursement between the two countries.

Our overall conclusions from these three reports are:

- There is some evidence that SCS added to CMM is cost-effective at moderate (<$20,000/QALY) ICER levels compared with CMM alone and/or reoperation.
- SCS cost-effectiveness increases and may be dominant over time compared with CMM and/or reoperation assuming device longevity of 4 years (base case) and at least a 30% pain threshold criteria. While there is evidence that the 30% pain threshold is met in the short term (up to 2 or 3 years), the assumption of continued efficacy past 3 years is questionable from the only RCT reporting pain 5-10 years after implantation.
- Only one study was conducted in a US setting. Differences in health care systems and reimbursement in the UK make transferring results from their economic evaluations The US study was underpowered, included only hospital charges, and did not consider CMM as an alternative to SCS.

Washington State Agency Data

The following data is provided by the Washington State agencies on their utilization and cost information.

Table 1. Washington State Health Care Agencies – Spinal Cord Stimulation (SCS) Patient Costs by Diagnosis, 2006-2009

Direct and related costs

Diagnosis Class	2006		2007		2008		2009		Total	
	#	Paid	#	Paid	#	Paid	#	Paid	#	Paid
Chronic Pain	16	$500,582	23	$1,335,587	40	$880,685	33	$686,423	122	$3,403,277
Failed Back Surg	51	$855,744	68	$1,239,056	87	$1,850,947	21	$410,802	232	$4,356,549
Other	6	$180,305	4	$6,718	9	$133,931	9	$27,979	30	$348,933
Regional Pain Syndrome	1	$21,372	4	$388,591	4	$28,392	5	$420,121	14	$858,476
Ischemia	0		0		1	$1,375	0		1	$1,375
SCS Malfunction	3	$45,466	13	$255,019	17	$251,177	9	$115,391	42	$667,053
Grand Total	**77**	**$1,603,469**	**112**	**$3,224,971**	**158**	**$3,146,507**	**77**	**$1,660,716**	**441**	**$9,635,663**

 # = unique patient/diagnosis combinations by year

Table 2. Washington State Health Care Agencies - 5 year Submitted vs. Reimbursed Costs for SCS, 2005-2009

Charges within a 3 day window of major procedure related by diagnosis

Neuropathic Pain - Direct CPT Costs only	Total Patients	Submitted Costs		Reimbursed Costs	
		Total	Average per patient	Total	Average per patient
UMP/PEP*	118	$12,464,150	$105,628	$4,686,442	$39,716
L&I	160	$7,638,103	$47,738	$3,674,754	$22,967
DSHS	21	$919,687	$43,795	$254,336	$12,111
Total	**299**	**$21,021,940**	**$70,307**	**$8,615,532**	**$28,814**

**UMP/PEP costs include only direct costs by related CPT/HCPCS codes.*

UMP/PEP Detailed Data Review

UMP/PEP data was summarized for adverse events and relationships between procedures, but other WA state agencies (L&I, DSHS), due to differences in patient management and data availability, were not. L&I data was part of an internal observational study; outcome and economic results were systematically captured for publication with much more detail than available in their administrative data. DSHS data had very low patient counts, and limited patient continuity which did not lend itself to more detailed analysis.

For the five years under review (2005-2009), UMP/PEP paid for a total of 118 patients to undergo SCS procedures. On average, these patients had 4.3 (SD=1.8) different surgical encounters, and had spinal cord stimulators implanted for an average of 25.5 (SD=15.3) months. The average total cost per month of implantation was $2959* (SD=$5564) and the average total cost per patient over all months of implantation was $54,353* (SD=$101,130). **Total costs of SCS device implantation include CPT codes for implantation, revision and removal, programming, electrode and battery replacement, adverse events, and associated tests and treatments*

TABLE 3a. UMP/PEP SCS Adverse Events Summary (including revision/removal) 2005-2009

Event Type	Adverse Events				Adverse Events Total	Emergency Room Visits	Revision/ Removals
	Reactions	Device Malfunctions	Comp.of Neuro Device	Infections/ Wounds			
Patients	6	17	5	5	33	8	27
% of patients	5%	14%	4%	4%	28%	7%	23%
Occurrences	6	23	8	11	48	19	84
Total cost	$254,177	$220,118	$210,927	$128,086	$813,308	$8,593	$205,183
Avg cost/ occurrence	$42,353	$9,570	$26,366	$11,644	$24,646	$452	$2,443
Cost range	$105-$248,232	$190-$42,323	$806-$121,738	$13-$98,759	$13-$248,232	$12-$756	$77 - $10,642

**Reactions – Lumbar Puncture Reaction, Reaction to Device, Urticaria, Other Reaction*
**Infections/Wounds – Open wounds, post-op infections, acute post-op pain*
Note that the rate of adverse events may be under-reported due to unclear data capture in 2005, as only one adverse event was recorded in all patients.

TABLE 3b. UMP/PEP Failed SCS Trial Costs vs. Implantation Costs, 2005-2009, Average treatment duration 22 months

SCS Trial Only vs Trial plus Implant	Count	Failure/ Success Rates	Total cost	Min	Max	Pt Avg
Failed trial only pts	36	30%	$157,902	$0	$29,444	$4,386
Trial plus implant pts	82	68%	$6,201,349	$836	$571,677	$75,626

CHART 3c. UMP/PEP Months from SCS Implantation to Revision

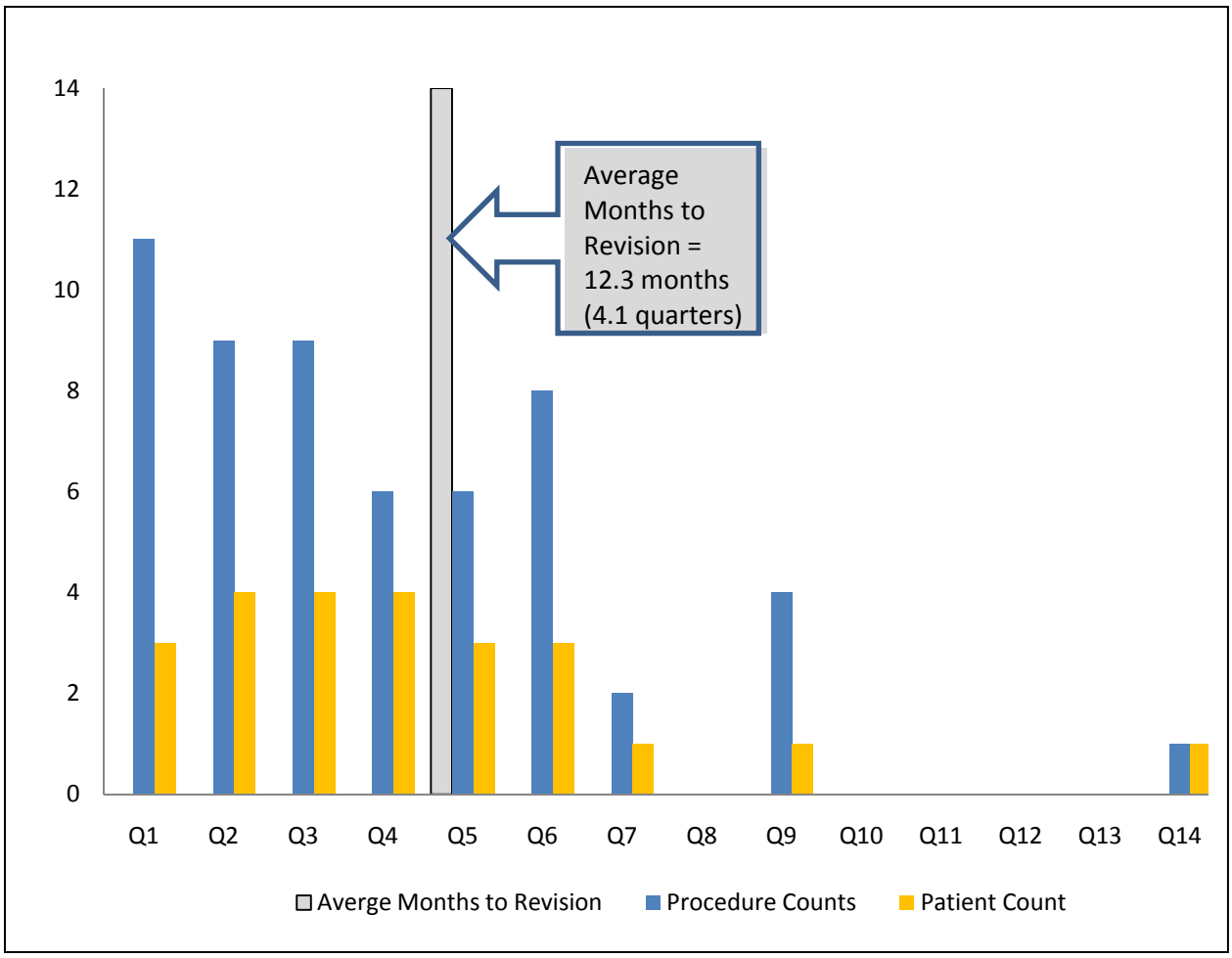


Chart represents only 25/118 patients (those with records of both implant and revision more than 1 month afterwards).

Related Medical Codes		
Codes	**Number**	**Description**
CPT	63650	Percutaneous implantation of neurostimulator electrode array, epidural
	63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
	63660	Revision or removal of pulse generator.
	63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling.
	63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver
ICD-9-Proc	03.93	Implantation or replacement of spinal neurostimulator lead(s)
	03.94	Removal of spinal neurostimulator lead(s)
	86.05	Incision with removal of foreign body or device from skin and subcutaneous tissue
	86.94	Insertion or replacement of single-array neurostimulator pulse generator, not rechargeable
	86.95	Insertion or replacement of dual-array neurostimulator pulse generator, not rechargeable.
	86.97	Insertion or replacement of single-array rechargeable neurostimulator pulse generator
	86.98	Insertion or replacement of dual-array rechargeable neruostimulator pulse generator
HCPCS II Device Codes	L8680	Implantable neurostimulator electrode, each
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery(internal) for use with implantable neurostimulator, replacement only
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	95971	Analyze Neurostim, Simple Programming
	95972	Analyze Neurostim, Complex Programming
	95973	Analyze Neurostim, complex programming, each addntl ½ hr

Medicare C codes	C1767	Generator, neurostimulator (implantable) non-rechargeable
	C1820	Generator, neruostimulator (implantable) with rechargeable battery and charging system
	C1883	Adaptor/extension, pacing lead or neurostimularo lead (implantable)
	C1778	Lead, neurostimulator (implantable)
	C1897	Lead, neurostimulator, test kit (implantable)
	C1787	Patient programmer, neurostimulator
	C1816	Receiver and/or transmitter, neurostimulator (implantable)
	E0752	Neurostimulator electrode
	E0754	Neurostimulator patient programmable interface
ICD-9 Diag	V53.02	Fitting and adjustment of neuropacemaker (brain, peripheral nerve, spinal cord)

Summary for key question 4:

What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

We included three complete economic evaluations; two were published economic evaluations of SCS compared with other interventions for pain and one was included as part of the recent HTA conducted by NICE in the UK. 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 reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) 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.

Table 9. Summaries of economic studies.

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions
Taylor & Taylor (2005)[95]	CUA SCS versus CMM (indirect comparison)	Hypothetical population derived from two different RCTs: • FBSS patients (for SCS) • chronic leg and back pain patients (for CMM) **Clinical Data:** **SCS:** Proportion of pts receiving SCS implant; Four health states: optimal or suboptimal pain relief with or without complications **CMM**: Two health states: optimal or suboptimal pain relief (assumed no complications) **Data sources:** two RCTs **Costs** **SCS** implantation; SCS complications; reimplantation; annual maintenance. **CMM**: costs, maintenance **Data sources:** published literature (Kumar 2002) **Utility:** **Data sources:** published literature	**Short-term (first 2 years):** Decision tree **Lifetime:** Markov model **Sensitivity analysis:** Univariate and multivariate analysis across a range of parameter values: • SCS screening • SCS complications • SCS battery life • SCS failure • SCS and CMM effectiveness • Life expectancy **Strengths:** • length of follow-up **Weaknesses:** • healthcare perspective (not societal) • indirect comparisons made from two RCTs	**2-year costs (€*):** **SCS**: 16,250 (+3002 vs CMM) **CMM:** 13,248 **2-year utility (QALYs/patient):** **SCS**: 0.67 (+0.066 vs CMM) **CMM:** 0.604 **2-year ICER:** €45,819/QALY **Lifetime costs (€*):** **SCS**: 75,758 **CMM:** 122,725 **Lifetime utility (QALYs/patient):** **SCS**: 15.91 (+1.12 vs CMM) **CMM:** 14.79 **Lifetime ICER:** SCS dominant	**2-year ICER:** 30,370 – 63,511/QALY (model most sensitive to SCS effectiveness and complication rate) **Lifetime ICER:** SCS dominant at all levels	**Short-term:** SCS may be cost-effective, but more data are needed to generate a more precise estimate. **Lifetime:** SCS is more effective and less costly than CMM.

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions
North 2007[98]	CUA, CEA SCS versus reoperation	FBSS patients (40 of the first 42) from North 2005 RCT[14] **Clinical Data:** Primary: frequency of crossover Secondary: success (≥ 50% pain relief and patient satisfaction) **Data sources:** North 2005 RCT[14] **Costs** Admission, room & board, OR, pharmacy, radiology, lab, med/surg supplies, PT/OT/RT, other (eg., anesthesia) **Data sources:** charge data from hospital billing department **Utility:** Assigned 0.83 for success and -.59 for failure, QALYs calculated using time spend within each utility assuming no survival advantage **Data sources:** published literature	**Primary analyses:** • Intent-to-treat • Treat-as-intended (crossovers considered failures) • Per-protocol (final treatment) • Crossover patients only (not included here) **Sensitivity analysis:** Bias-corrected nonparametric bootstrapping using 1000 randomly derived samples **Strengths:** • RCT design • Data from a single hospital in the US **Weaknesses:** • Small sample size • No CMM comparator • Short-term analysis only (mean follow-up: 3.1 years)	***Intent-to-treat:*** SCS dominant for both ICER and ICUR **Costs ($) (mean of 3.1 years)** **SCS**: 31,530 ± 3,782 (-6,629 (95% CI, -17,754, 4,148) versus reoperation (*P* = .234) **Reoperation:** 38,160 ± 3,932 **Mean QALYs:** **SCS**: 2.14 ± 0.08 (+0.104 (95% CI, -0.15, 0.24) versus reoperation (*P* = .660) **Reoperation:** 2.10 ± 0.07 **Success:** **SCS:** 37% (7/19) ARR = 3.15% (95% CI, -26.1, 33); *P* = .816 **Reoperation:** 33% (7/21) - - - - - - - - - - - - - ***Treated-as-intended (crossover = failure):*** SCS dominant for both ICER and ICUR **Costs ($) (mean of 3.1 years)** **SCS**: 31,530 ± 3,782 (-6,629 (95% CI, -17,754, 4,148) versus reoperation (*P* = .234) **Reoperation:** 38,160 ± 3,932 **Mean QALYs:** **SCS**: 2.25 ± 0.09 (+0.16 (95% CI, -0.13, 0.45) versus reoperation (*P* = .273) **Reoperation:** 2.09 ± 0.10 **Success:** **SCS:** 37% (7/19) ARR = 27.3% (95% CI, 2.2, 52.3); *P* = .038 **Reoperation:** 10% (2/21)	***Intent-to-treat:*** SCS dominant for cost-effectiveness ~72% of SCS results are below the $40,000/QALY "maximum willingness to pay" cost-effectiveness threshold often used by US policymakers ***Treated-as-intended:*** NR ***Per-protocol:*** NR	SCS should be the initial therapy of choice for FBSS patients, as it was more effective and less costly than reoperation. The cost-effectiveness of SCS is best when repeat operation is avoided. Reoperation has a low rate of success should SCS fail.

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions
North 2007 (continued)				- - - - - - - - - - - - - ***Per-protocol (final treatment):*** SCS dominant for both ICER and ICUR **Costs (mean 3.1 yrs)** **SCS**: 34,371 ± 3,060 (-1,970 (95% CI, -14,045, 10,696) versus reoperation (*P* = .754) **Reoperation:** 36,341 ± 5,782 **Mean QALYs:** **SCS**: 2.18 ± 0.06 (+0.18 (95% CI, -0.03, 0.35) versus reoperation (*P* = .09) **Reoperation:** 2.00 ± 0.07 **Success:** **SCS:** 45% (12/27) ARR = 29% (95% CI, 2, 56); *P* = .07 **Reoperation:** 15% (2/13)		

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions
Simpson 2009 (NHS)[36]	**Manufacturer model (submitted by ABHI):** CUA SCS + CMM versus (1) CMM, or (2) reoperation	FBSS or CRPS patients **Clinical Data:** Success: ≥ 50% pain reduction Six health states: optimal, suboptimal, or no perceived pain relief with or without complications **Data sources:** FBSS: 2 RCTs[13, 14] CRPS: 1 RCT[25] **Costs** Screening, implant, failed screening, device explant, reimplant, adverse events **Data sources:** PROCESS trial **Utility:** EQ-5D derived values: No pain reduction = 0.168; Suboptimal pain relief or optimal pain relief with complications = 0.258; Optimal pain relief = 0.598 **Data sources:** PROCESS trial	**Short-term (6 months direct observation):** Decision tree **Lifetime:** Markov model **Sensitivity analysis:** Probabilistic **Strengths:** • NHS-perspective • RCT-based **Weaknesses:** • UK-based, applicability to US-setting	***50% pain threshold criteria*** ***FBSS: SCS + CMM versus CMM*** **Cost difference:** £11,439 (base case 4-year device longevity only) **QALYs difference:** 1.25 (base case 4-year device longevity only) **ICER:** base case 4-year device longevity: £9155 2-year device longevity: £30,285 7-year device longevity: £2745 Device longevity > 7 years: SCS + CMM dominant - ***FBSS: SCS + CMM versus reoperation*** **Cost difference:** £10,651 (base case 4-year device longevity only) **QALYs difference:** 1.34 (base case 4-year device longevity only) **ICER:** base case 4-year device longevity: £7954 2-year device longevity: £26,445 7-year device longevity: £2362 Device longevity > 7 years: SCS + CMM dominant	***FBSS: SCS + CMM versus CMM*** SCS produces more QALYs Probability of SCS +CMM being cost-effective on 15-year horizon ((based on ABHI report): • ~80% (when threshold set at £20,000/QALY) • >95% (when threshold set at £30,000/QALY) - - - - - - - - - - - - - - - - - - ***FBSS: SCS + CMM versus reoperation*** SCS produces more QALYs Probability of SCS +CMM being cost-effective on 15-year horizon (based on ABHI report): • >90% (when threshold set at £20,000/QALY) • ~98% (when threshold set at £30,000/QALY) - - - - - - - - - - - - - - - - - - ***CRPS: SCS + CMM versus CMM*** Probability of SCS +CMM being cost-effective on 15-year horizon (based on ABHI report): • >40% (when threshold set at £20,000/QALY) • >60% (when threshold set at £30,000/QALY)	SCS is more effective and less costly than CMM.

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions
(Simpson 2009 continued)				(continued) - ***CRPS: SCS + CMM versus CMM*** **Cost difference:** £12,041 (base case 4-year device longevity only) **QALYs difference:** 0.64 (base case 4-year device longevity only) **ICER:** base case 4-year device longevity: £18,881 2-year device longevity: £28,015 7-year device longevity: £1607 Device longevity > 7 years: SCS + CMM dominant		

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions
Simpson 2009 (NHS)[36]	**ScHARR model:** CUA SCS + CMM versus CMM, or reoperation	FBSS or CRPS patients **Clinical Data:** Optimal pain relief: ≥ 50% pain reduction FBSS: Five health states: optimal pain relief, suboptimal pain relief, no pain relief (SCS), no pain relief (surgery), dead (any cause) CRPS: Four health states: optimal pain relief, suboptimal pain relief, no pain relief (SCS), dead (any cause) **Data sources:** FBSS: 2 RCTs[13, 14] CRPS: 1 RCT[25] **Costs** Medication, consultations, stimulation, implantation, complications, explantation, failed trial stimulation **Data sources:** NHS cost schedules and published literature **Utility:** EQ-5D derived values: No pain reduction = 0.168; Suboptimal pain relief or optimal pain relief with complications = 0.258;	**Short-term (6 months direct observation):** Decision tree **Lifetime:** Markov model **Sensitivity analysis:** Probabilistic **Strengths:** • NHS-perspective • RCT-based **Weaknesses:** • UK-based, applicability to US-setting	**All results based on 4-year device longevity and 15-year time horizon)** ***FBSS: SCS + CMM versus CMM*** **Cost difference:** £10,035 (favoring SCS) **QALYs difference:** 1.26 (favoring SCS) **ICER:** £10,035 (SCS + CMM dominant) - ***FBSS: SCS + CMM versus reoperation*** **Cost difference:** £9,430 (favoring SCS) **QALYs difference:** 1.34 (favoring SCS) **ICER:** £7,043 (SCS + CMM dominant) - ***CRPS: SCS + CMM versus CMM*** **Cost difference:** £8,775 (favoring SCS) **QALYs difference:** 0.35 (favoring SCS) **ICER:** £25,095 (SCS + CMM dominant)	***FBSS: SCS + CMM versus CMM*** SCS produces more QALYs Probability of SCS +CMM being cost-effective on 15-year horizon (based on ABHI report): • 99.02% (when threshold set at £20,000/QALY) • 99.96% (when threshold set at £30,000/QALY) - - - - - - - - - - - - - - - - - - ***FBSS: SCS + CMM versus reoperation*** SCS produces more QALYs Probability of SCS +CMM being cost-effective on 15-year horizon (based on ABHI report): • 100% (when threshold set at £20,000/QALY) - - - - - - - - - - - - - - - - - - ***CRPS: SCS + CMM versus CMM*** Probability of SCS +CMM being cost-effective on 15-year horizon (based on ABHI report): • 78.36% (when threshold set at £20,000/QALY) • 97.38% (when	SCS is more effective and less costly than CMM.

Study	Design	Population & Model inputs	Methods of analysis/ strengths and limitations	Relevant results	Results of sensitivity analysis	Author conclusions
		Optimal pain relief = 0.598 **Data sources:** PROCESS trial			threshold set at £30,000/QALY)	

ARR: absolute risk reduction
CMM: conventional medical management
ICER: incremental cost-effectiveness ratio
ICUR: incremental cost-utility ratio
NR: not reported
QALY: quality-adjusted life year
SCS: spinal cord stimulation
* in 2003 Euros

5. Summary and Implications

Results

For key question 1, we identified a total of three RCTs and one prospective cohort study. One RCT included only patients with complex regional pain syndrome (CRPS-I); two RCTs included only patients with failed back surgery syndrome (FBSS). The prospective cohort study was conducted specifically on patients with open Washington state workers' compensation claims. For key question 2, we identified six additional case series, all with mid-term follow-up. For key question 3, we identified four prospective and two retrospective cohort studies. We identified three cost-effectiveness analyses to address key question 4.

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

One RCT provided data on the short-term efficacy of SCS compared with physical therapy in complex regional pain syndrome (CRPS) patients. Two RCTs reported on the efficacy of SCS in patients with failed back surgery syndrome (FBSS): one RCT provided data on both the short- and mid-term efficacy of SCS and conventional medical management (CMM) compared with CMM alone, while another provided data on the short-term efficacy of SCS compared with lumbar reoperation. Heterogeneity between these studies prevented pooling of the data. In general, the RCTs reported significantly improved outcomes in the short-term for patients randomized to receive SCS than those randomized to the control groups; however, results were mixed at the mid-term follow-up in the one RCT reporting results after five years.

One prospective cohort study provided data on the short-term effectiveness of SCS compared with Pain Clinic and Usual Care treatments in FBSS patients with open workers' compensation claims in the State of Washington. In general, the cohort study found no differences in outcomes between patients in the SCS and two control groups.

"Success" from a composite score

Efficacy: One RCT found that patients randomized to receive SCS had significantly improved "success" (a composite of pain relief and patient satisfaction) compared with those randomized to undergo lumbar reoperation at mean of 2.9 years follow-up.

Effectiveness: The prospective cohort study on workers' compensation patients found no difference between SCS, pain clinic (PC), or usual care (UC) groups at any follow-up up to 24 months in the percent of patients achieving the primary outcome composite measure of success (includes pain, function, and medication usage components).

Pain relief

Efficacy: Patients randomized to receive SCS had significantly improved pain relief compared with those randomized to undergo control treatments in two RCTs with ≤ 2 year follow-up. One of these RCTs reported that the differences between groups in both the change in VAS scores

(from baseline) and in mean VAS scores were no longer statistically significant by three to five years post-implantation.

Effectiveness: The prospective cohort study on workers' compensation patients reported that significantly more patients in the SCS group achieved ≥ 50% leg pain relief by six months than those in the UC group, there was no difference between the SCS and PC group at the same follow-up; furthermore, no differences were identified between groups in the percentage of patients achieving leg pain relief of ≥ 50% or more at the 12- and 24-month follow-ups.

Function

Efficacy: One RCT found that patients in the SCS group had significantly better Oswestry Disability Index scores than those in the CMM group at six months follow-up. Another RCT reported no significant differences between the SCS and reoperation groups in the neurological status or ability to perform daily activities a mean of 2.9 years follow-up, however, raw data were not provided.

Effectiveness: There were no significant differences in either the Roland-Morris Disability Questionnaire (RDQ) scores or ability to perform daily tasks between treatment groups in the prospective cohort study on workers' compensation patients.

Health-related quality of life (HR-QoL)

Efficacy: One RCT reported no difference in several QoL outcome measures between the SCS and physical therapy groups, including the mean percent change in quality of life at the 6- and 24- month follow-ups as well as the Nottingham Health Profile, EQ-5D (EuroQol-5D), and Self-Rating Depression Scale scores at five years. Another RCT reported that patients randomized to receive SCS had significantly better scores in seven of the eight SF-36 (Short-Form 36) outcome scales compared with those randomized to receive CMM at six months. The same RCT reported that the six-month EQ-5D utility scores were significantly better in the SCS compared with the CMM group. Further, no difference was found between groups in the rate of patients (not working at baseline) who had returned to work by six months.

Effectiveness: The prospective cohort study on workers' compensation patients reported no significant differences between treatment groups in SF-36 scores and work/disability status.

Patient satisfaction and perceived effect

Efficacy: One RCT reported that significantly more patients in the SCS group were satisfied with both their level of pain relief and with their treatment in general than those in the CMM group at six months follow-up. Another RCT incorporated patient satisfaction with pain relief into a composite outcome, "success", which was reported above. Another RCT reported global perceived effect (GPE) scores. Significantly more patients in the SCS group reported GPE of "much improved" or "best ever" at both the 6- and 24- month follow-ups compared with the physical therapy group; however the differences between groups were no longer statistically significant by five years.

Medication usage

Efficacy: One RCT reported no differences at six months between the SCS and CMM groups in the percentage of patients using opioids, non-steroidal anti-inflammatory medications, or antidepressants; however, significantly fewer SCS patients were taking anticonvulsants than those in the CMM group. There were no differences between the SCS and CMM groups in the percentage of patients using all reported non-drug therapies (eg., physical or psychological rehabilitation, acupuncture, or massage) except for TENS (transcutaneous electrical nerve stimulation), for which the rate of use was lower in SCS compared with CMM patients. Another RCT found that significantly more patients in the SCS group were taking a stable or decreased dosage of opioids (versus baseline) than those in the reoperation group at a mean of 2.9 years follow-up.

Effectiveness: Although significantly fewer patients in the SCS group used opioids on a less than daily basis than did those in the PC group at six months, no other significant differences between treatment groups were identified in the prospective cohort study on workers' compensation patients.

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

Short-term (< 5 years) safety data were reported by three RCTs and one prospective cohort study; mid-term (5–10 years) safety data were reported by one RCT and six case series. No long-term safety data were available.

Revision

All three RCTs and the one cohort study reported short-term revision rates of SCS devices; one RCT and all six case series reported mid-term revision rates. However, each study reported the data differently, and not all studies reported an overall revision rate (the proportion of patients with one or more revision). Therefore, revision rates were difficult to pool. Reasons for revision included (but were not limited to): revision or replacement of electrodes/leads due to migration, improvement of paresthesia, defective electrodes, infection, fractured electrode, or hardware malfunction; revision or replacement of generators (or stimulators) due to painful pulse generator pockets, migration, battery depletion, defective generator, electrical leak, or failure; revision of the connecting cable/lead due to fracture, discomfort, or insulation damage; SCS systems were explanted (and often reimplanted) due to infection, recurrent rejection, discomfort, ineffective pain relief, new intolerable pain, defective transmitters, or seizures.

Other SCS-related complications or side effects

Complications or side effects ascribed to the SCS device were reported by two RCTs, one cohort study, and six case series; overall short-term rates ranged from 8–100% of patients. At two years follow-up, one RCT reported that side effects had occurred in 100% of available SCS patient; another RCT reported device-related complications not requiring revision in 14% of patients. Complications or side effects ascribed to the SCS system included: change in amplitude by bodily movements, paresthesia in other body parts, pain or irritation from pulse generator, disturbed urination, movements or cramps resulting from elevated amplitute, infection, loss of

therapeutic effect, loss of parasthesia, or unpleasant paresthesia, subcutaneous hematoma, cerebrospinal fluid leak, dural puncture, or pain over SCS components.

Complications not related to SCS

Complications not related to SCS were reported by one RCT. Rates of new illness, injury, or condition and of worsening of the pre-existing condition were similar for both the SCS and the CMM group; however the percentage of patients that had experienced drug adverse events or extra pain events were 15 to 23% higher in the CMM group than in the SCS group at one year.

Mortality

Short-term mortality data were obtained from three RCTs and one prospective cohort study. Two deaths occurred in the SCS groups (2/139); one due to a sudden cardiac event at six months and another between six and twelve months for which the cause was not reported. No deaths occurred in any of the control groups (0/179). Mid-term mortality data were obtained from one RCT and three case-series. Two deaths occurred in SCS patients; one due to cerebrovascular accident in a patient being treated for angina, not neuropathic pain, and another due to suicide. No deaths were attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.

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

We identified six small prognostic studies (four prospective and two retrospective studies). In general, very little evidence was found that suggests that any of the factors evaluated were strongly associated with improved outcome following SCS. Prognostic factors evaluated included:

Age

Three studies evaluated whether age had an effect on pain relief in the first year following implantation. While one study reported that younger age was significantly associated with improved pain relief, two other studies found no association between patient age and pain relief. Furthermore, one prospective cohort study demonstrated that age was not correlated with SF-36 or GPE scores at nine months

Sex

Four studies evaluated the effect of patient sex on pain relief following SCS. Three studies found that sex was not predictive of pain relief in the first year, and one study reported that success at five years was significantly higher in females. This study also reported that females had significant improvements in a combination of everyday activities (ability to work, walk, climb stairs, sleep, have sex, drive, and eat), neurological function (strength, sensation, and bladder/bowel control), and medication use. One other study found no correlation between patient sex and SF-36 or GPE scores at nine months.

Workers' compensation or other disability payments
One study found no difference in the percentage of patients who achieved at least 50% pain relief at three months between those receiving workers' compensation or other disability payments than those not under such programs.

Duration of pain
Two studies evaluated and found no relationship between duration of chronic pain and pain relief in the first year following SCS implantation. One study reported that CRPS patients with a longer duration of chronic pain had significant improvements in quality of life at nine months as measured by two (of eight) domains of the SF-36 outcome measure by multivariate analysis; however, no association was found between pain duration and GPE scores.

Pain intensity
One study evaluated and found no association between the pain intensity at baseline and pain relief at one year.

Time since first lumbar surgery
One study found that the time since the first lumbar surgery was not associated with success or a composite score that included everyday activities, neurological function, and medication use at five years.

Number of prior operations for pain
Two studies evaluated and found no association between the number of previous operations for chronic pain and pain relief at three months or success at five years.

Pain location
Four studies evaluated and found no association between pain location and pain relief at follow-up, though each study compared different locations. One study reported no association between hand versus foot pain with nine-month SF-36 or GPE scores; another study found no difference in a combination of everyday activities, neurological function, and medication use between patients with axial versus radicular pain.

Laterality of pain
One study suggested that more SCS patients with unilateral pain achieved leg pain relief of at least 50% than did those patients with bilateral pain; similarly, more patients with unilateral pain had functional improvement (as measured by the RDQ) compared with those patients with bilateral pain.

Allodynia or hyposthesia at baseline
One retrospective study demonstrated that the absence of brush-evoked allodynia at baseline was significantly associated with success at one-year. In contrast, the presence of mechanical hypoesthesia at baseline was not correlated with success.

McGill Pain Questionnaire
Two studies evaluated the predictive effect of baseline McGill Pain Questionnaire scores with conflicting results. While one study found that higher McGill evaluative subscores were

associated with improved pain relief, the other study found that none of the domains of the McGill Pain Questionnaire were predictive of success at five years.

Minnesota Multiphasic Personality Inventory (MMPI)
Two studies evaluated whether MMPI scores at baseline were associated with improved pain relief. One study found that lower scores for the depression subscale were significantly correlated with pain relief at three months, while the other study found no correlation between MMPI scores and pain relief at a mean of 3.5 years.

SF-36 Mental Health Component
One study found that SCS patients with baseline SF-36 Mental Health scores in the top third of patients had better pain relief and functional outcomes (as measured by the RDQ) compared with those patients with baseline scores in the lowest third.

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

We included three complete economic evaluations; two were published economic evaluations of SCS compared with other interventions for pain and one was included as part of the recent HTA conducted by NICE in the UK. 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 reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) 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.

Table 10. Summary of evidence for Key Question 1.

Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?					
SCS	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Efficacy (Short-term: < 5 years)	**Moderate**	• **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 reoperation) 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 o 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).	+	-	+
	Low	• **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.	+	-	-
(Mid-term: 5 to < 10 years)	**Low**	• **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.	+	–	NA
(Long-term: ≥ 10 years)	**No evidence**	• There are no data available to assess long-term efficacy.	none	none	none
2. Effectiveness (Short-term: < 5 years)	**Low**	• **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 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	+	–	NA

		persist at the 12 month or 24 month evaluation.			
(Mid & Long-term: ≥ 5 years)	**No evidence**	• There are no data available to assess mid- or long-term effectiveness.	none	none	none

NA: not applicable

Table 11. Summary of evidence for Key Question 2.

Key Question 2: What is the evidence of the safety of spinal cord stimulation?					
SCS	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
1. Revision	**High**	• 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	**Moderate**	• 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	**High**	• 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.	+	+	+

Table 12. Summary of evidence for Key Question 3.

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?					
SCS	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
Summary: **There is no moderate or high evidence that any of the factors evaluated were associated with improved outcome following SCS.**					
1. Age	**Low**	• 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	**Low**	• 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	**Low**	• 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.	+	–	NA
4. Duration of pain	**Moderate**	• 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	**Low**	• There is low evidence from one cohort study to suggest that pain intensity at baseline is not associated with success.	+	–	NA
6. Time since first lumbar surgery	**Low**	• There is low evidence from one cohort study to suggest that time since first lumbar surgery is not predictive of success.	+	–	NA

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?					
SCS	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
7. Number of prior surgeries for pain	**Moderate**	• 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	**Low**	• There is low evidence from four cohort studies that pain location does not affect outcomes.	+	-	-
9. Laterality of pain	**Low**	• 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.	+	–	NA
10. Allodynia or hypoesthesia at baseline	**Low**	• There is low evidence from one cohort study that the presence of allodynia at baseline negatively correlates with success at one year, while the presence of hypoesthesia at baseline was not predictive of success.	+	–	NA
11. McGill Pain Questionnaire	**Low**	• 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)	**Low**	• 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	**Low**	• 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.	+	–	NA

Table 13. Summary of evidence for Key Question 4.

Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?					
SCS	**Strength of evidence**	**Conclusions/Comments**	**Quality**	**Quantity**	**Consistency**
Cost-effectiveness	**Moderate**	• 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 reoperation 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 reoperation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or reoperation) 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.	+	-	+

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90. Coffey, R. J., Owens, M. L., Broste, S. K. et al.: Mortality associated with implantation and management of intrathecal opiod drug infusion systems to treat noncancer pain. Anesthesiology, **111:** 881, 2009

91. Burchiel, K. J., Anderson, V. C., Wilson, B. J. et al.: Prognostic factors of spinal cord stimulation for chronic back and leg pain. Neurosurgery, **36:** 1101, 1995

92. van Eijs, F., Smits, H., Geurts, J. W. et al.: Brush-evoked allodynia predicts outcome of spinal cord stimulation in complex regional pain syndrome type 1. Eur J Pain, **14:** 164, 2010

93. North, R. B., Ewend, M. G., Lawton, M. T. et al.: Failed back surgery syndrome: 5-year follow-up after spinal cord stimulator implantation. Neurosurgery, **28:** 692, 1991

94. North, R. B., Kidd, D. H., Wimberly, R. L. et al.: Prognostic value of psychological testing in patients undergoing spinal cord stimulation: a prospective study. Neurosurgery, **39:** 301, 1996

95. Taylor, R. J., Taylor, R. S.: Spinal cord stimulation for failed back surgery syndrome: a decision-analytic model and cost-effectiveness analysis. Int J Technol Assess Health Care, **21:** 351, 2005

96. North, R. B., Kidd, D. H., Olin, J. et al.: Spinal cord stimulation for axial low back pain: a prospective, controlled trial comparing dual with single percutaneous electrodes. Spine (Phila Pa 1976), **30:** 1412, 2005

97. Fritzell, P., Hagg, O., Wessberg, P. et al.: 2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine (Phila Pa 1976), **26:** 2521, 2001

98. North, R. B., Kidd, D., Shipley, J. et al.: Spinal cord stimulation versus reoperation for failed back surgery syndrome: a cost effectiveness and cost utility analysis based on a randomized, controlled trial. Neurosurgery, **61:** 361, 2007

99. Ofman, J. J., Sullivan, S. D., Neumann, P. J. et al.: Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm, **9:** 53, 2003

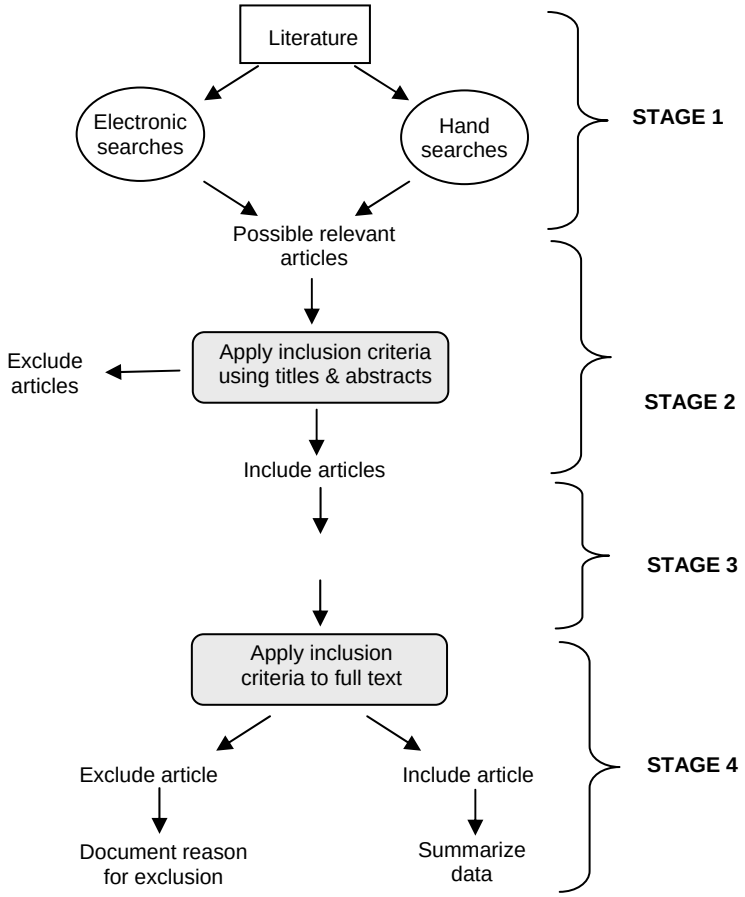
100. Chiou, C. F., Hay, J. W., Wallace, J. F. et al.: Development and validation of a grading system for the quality of cost-effectiveness studies. Med Care, **41:** 32, 2003

101. Baron, J. A., Weiderpass, E.: An introduction to epidemiological research with medical databases. Ann Epidemiol, **10:** 200, 2000

102. Lange, L. L., Jacox, A.: Using large data bases in nursing and health policy research. J Prof Nurs, **9:** 204, 1993

103. Cowper, D. C., Hynes, D. M., Kubal, J. D. et al.: Using administrative databases for outcomes research: select examples from VA Health Services Research and Development. J Med Syst, **23:** 249, 1999

Appendix A. ALGORITHM FOR ARTICLE SELECTION



Appendix B. SEARCH STRATEGIES

Database: MEDLINE
Search performed 2/24/10, repeated 5/16/10 to screen for additional studies (one found)

LIMITS: Humans, English, All Adult: 19+ years

1	Spinal cord stimulation
2	Chronic pain
3	#1 AND #2
4	Neuropathic pain
5	Ischemic pain
6	Ischaemic pain
7	Failed back surgery syndrome
8	Complex regional pain syndrome
9	Dystrophy
10	Causalgia
11	Phantom limb pain
12	Central pain
13	Stroke pain
14	Post-stroke pain
15	Diabetic neuropathy
16	Herpetic neuralgia
17	Post-herpetic neuralgia
18	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	#1 AND #18
20	**#3 OR #19 (FINAL SEARCH CODE)**

Keyword searches ("spinal cord stimulation") were conducted to search the EMBASE and Cochrane Library and others listed below.

Electronic Database Searches
The following databases have been searched for relevant information through the end of January, 2010:
Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Computer Retrieval of Information on Scientific Projects (CRISP)
Database of Reviews of Effectiveness (Cochrane Library)
EMBASE
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database
HSTAT (Health Services/Technology Assessment Text)

EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases
AHRQ- Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

Appendix C. EXCLUDED ARTICLES

Exclude at full-text review

Efficacy/ effectiveness:

Study	Reason for exclusion
1. Dario 2001	not a comparative study
2. Harke 2005	not a true comparative study (compares outcomes at 12 months to the response during the 45 minute SCS inactivation tests)
3. Hassenbusch 1995	confounding by indication (assigned treatment based on differential diagnosis)
4. Kemler 2001	no clinical outcomes reported (experimental measures of pain)
5. Monhemius 2003	N < 10 (only ended up with 6 pts)
6. North 1995	earlier f/u of North 2005
7. Taylor 2006 Eur J Pain	Systematic review
8. Taylor 2006 J Pain Sympt Manage	Systematic review
9. Tesfaye 1996	case series (no control)
10. Turner 1995	Systematic review

Safety:

Study	Reason for exclusion
1. Coffey 2009	Pain diagnosis NR (≥75% of patients need to be diagnosed with neuropathic pain for inclusion)
2. Devulder 1991	Mean f/u NR (needs to be ≥ 5 years for inclusion)
3. Devulder 1997	Mean f/u < 5 years (mean period of use was 4.9 years)
4. Fiume 1995	Mean f/u < 5 years (mean 55 months)
5. Heidecke 2000	Mean f/u < 5 years (mean 46 months)
6. Krainick 1980	Mean f/u NR (needs to be ≥ 5 years for inclusion)
7. Kumar 1996 (15-yr experience)	Earlier f/u of Kumar & Wilson 2007
8. Kumar 1998	Earlier f/u of Kumar & Wilson 2007
9. Kumar 2006 (Complications of SCS, suggestions…)	Mean f/u < 5 years (mean 41.6 months)
10. Kumar 2006 (22-yr experience)	Earlier f/u of Kumar & Wilson 2007
11. Lang 1997	<75% of patients had neuropathic pain (67%)
12. LeRoy 1981	Mean f/u < 5 years (mean 30.7 months)
13. Long 1981	Pain diagnosis NR (≥75% of patients need to be diagnosed with neuropathic pain for inclusion)
14. Manca 2008	No safety data (overlaps with Kumar 2007 PROCESS)
15. Mittal 1987	Mean f/u NR (needs to be ≥ 5 years for inclusion)
16. North & Campbell 1991	No complications reported
17. North & Ewend 1991	Mean f/u < 5 years (data used for complications had a mean f/u of 2.2 years)
18. Quigley 2003	Mean f/u < 5 years (mean 4.2 years)
19. Rosenow 2006	Mean f/u < 5 years (mean 485 days)
20. Simpson 1991	Mean f/u < 5 years (median 29 months)

Special populations:

Study	Reason for exclusion
1. Allegri 2004	LoE III (prospective, f/u NR, no multivariate analysis)
2. Brandwin 1982	<75% of patients had neuropathic pain (50% had "movement disorders")
3. Broggi 1994	LoE III (retrospective, no multivariate analysis)
4. Cioni 1995	N < 10 (N = 9)
5. Daniel 1985	No relevant prognostic factors evaluated (only one was reviewer's prediction)
6. De La Porte 1993	LoE III (retrospective, no multivariate analysis)
7. Devulder 1991	LoE III (retrospective, no multivariate analysis)
8. Fiume 1995	LoE III (retrospective, no multivariate analysis)
9. Hord 2003	n < 10 per group (one group had only 3 patients)
10. Kay 2001	LoE III (retrospective, no multivariate analysis)
11. Kim 2001	LoE III (retrospective, no multivariate analysis)
12. Koeze 1987	LoE III (retrospective, no multivariate analysis)
13. Kumar 1996	Overlaps with Kumar 2007
14. Kumar 1998	Overlaps with Kumar 2007
15. Kumar 2006 (22-year experience)	LoE III (retrospective, no multivariate analysis)
16. Kumar 2007	LoE III (retrospective, no multivariate analysis)
17. Kumar & Toth 1998	LoE III (retrospective, no multivariate analysis)
18. Kupers 1994	Pain diagnosis NR (≥75% of patients need to be diagnosed with neuropathic pain for inclusion)
19. Lang 1997	<75% of patients had neuropathic pain (67%)
20. Long 1981	LoE III (retrospective, no multivariate analysis)
21. Meilman 1989	n < 10 per group (one group had 7 patients)
22. North & Campbell 1991 (…repeated operation)	LoE III (retrospective, f/u < 80%)
23. North 1991 (SCS for chronic…)	LoE III (retrospective, no multivariate analysis)
24. North 1993	LoE III (retrospective, no multivariate analysis)
25. Pineda 1975	LoE III (retrospective, no multivariate analysis)
26. Sanchez-Ledesma 1989	LoE III (retrospective, no multivariate analysis)
27. Shimoji 1993	No prognosis data reported for the patients who received permanent SCS implants
28. Van de Kelft	LoE III (retrospective, no multivariate analysis, f/u < 80%)
29. Wester 1987	LoE III (retrospective, no multivariate analysis)

Appendix D. LEVEL AND STRENGTH OF EVIDENCE DETERMINATION

Each study was rated against pre-set criteria that resulted in an evidence rating (Level of Evidence I, II, III, or IV) and presented in a table. For therapeutic and prognostic articles, the criteria are listed in the Table below.

Definition of the different levels of evidence for articles on therapy and prognosis

	Studies of Therapy		Studies of Prognosis	
Level	**Study design**	**Criteria**	**Study design**	**Criteria**
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size	Good quality cohort	• Prospective design • Patients at similar point in the course of their disease or treatment • F/U rate of 80%+ • Patients followed long enough for outcomes to occur • Controlling for extraneous prognostic factors*
II	Moderate or poor quality RCT	• Violation of any of the criteria for good quality RCT	Moderate quality cohort	• Prospective design, with violation of one of the other criteria for good quality cohort study • Retrospective design, meeting all the rest of the criteria in level I
	Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data* in a retrospective study • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size • Controlling for possible confounding†		
III	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort	Poor quality cohort	• Prospective design with violation of 2 or more criteria for good quality cohort, or • Retrospective design with violation of 1 or more criteria for good quality cohort
	Case-control	• Any case-control design	Case-control	• Any case-control design
IV	Case series	• Any case series design	Case series	• Any case series design

* Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence for the relevant question or topic is determined. Methods for determining the overall strength of evidence for diagnostic studies are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (LoE), quantity of studies and consistency of results across studies as described by AHRQ[53].

The following definitions are used by SRI to determine whether or not the body of evidence meets the criteria for each domain:

Domain	Definition/Criterion
Quality	• At least 80% of the studies are LoE I or II
Quantity	• There are at least three studies which are adequately powered to answer the study question
Consistency	• Study results would lead to a similar conclusion (similar values, in the same direction) in at least 70% of the studies

Based on the criteria described above, the possible scenarios that would be encountered are described below. Each scenario is ranked according to the impact that future research is likely to have on both the overall estimates of an effect and the confidence in the estimate. This ranking describes the overall "Strength of Evidence" (SoE) for the body of literature on a specific topic. The method and descriptions of overall strength are adapted for diagnostic studies from system described by the GRADE Working Group[52] for the development of clinical guidelines.

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	**High**	Very unlikely to change confidence in effect estimate	+	+	+
2	**Moderate**	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	**Low**	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	**Very Low**	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al[99]. QHES embodies the primary components relevant for critical appraisal of economic studies[99, 100]. It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (eg, with respect to age, gender, medical conditions, etc)? To what extent are the populations for each intervention

comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (eg, complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (eg, similar protocols, follow-up procedures, evaluation of outcomes, etc)?
- How were the data and/or patients selected or sampled (eg, a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (eg, were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:
- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

QHES Instrument[99] **Study Taylor and Taylor**

Questions	Possible Points	Points Awarded
1. Was the study objective presented in a clear, specific, and measurable manner?	7	7
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	8
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	0
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	9
6. Was incremental analysis performed between alternatives for resources and costs?	6	6
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	5
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	8
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	6
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	7
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	6
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	8
16. Was there a statement disclosing the source of funding for the study?	3	3
TOTAL POINTS	**100**	**99**

QHES Instrument[99] **Study North**

Questions	Possible Points	Points Awarded
1. Was the study objective presented in a clear, specific, and measurable manner?	7	7
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	8
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	0
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	9
6. Was incremental analysis performed between alternatives for resources and costs?	6	6
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	5
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	0
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	0
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	6
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	0
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	0
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	0
16. Was there a statement disclosing the source of funding for the study?	3	3
TOTAL POINTS	**100**	**63**

QHES Instrument[99] **Study Simpson (scores applicable to both models presented)**

Questions	Possible Points	Points Awarded
1. Was the study objective presented in a clear, specific, and measurable manner?	7	7
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	8
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	0
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	9
6. Was incremental analysis performed between alternatives for resources and costs?	6	6
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	5
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	8
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	6
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	7
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	6
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	8
16. Was there a statement disclosing the source of funding for the study?	3	3
TOTAL POINTS	**100**	**99**

Appendix E. LEVEL OF EVIDENCE FOR COMPARATIVE STUDIES

Methodological quality of therapeutic studies evaluating efficacy or effectiveness following spinal cord stimulation.

Methodological principle	Kemler 2000, 2004, 2008	Kumar 2007, Manca 2008	North 2005	Turner 2010
Study design Randomized controlled trial Cohort study Case series	✓	✓	✓	✓
Statement of concealed allocation*	✓	✓	✓	
Intention to treat*	✓	✓	✓	
Independent or blind assessment	✓	✓	✓	✓
Cointerventions applied equally	✓	✓	✓	✓
Complete follow-up of ≥ 80%	✓	✓		✓
Adequate sample size	✓	✓	✓	✓
Controlling for possible confounding†	✓	✓		✓
Evidence class	**I**	**I**	**II**	**II**

* Applies to RCTs only.
† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Spectrum Research has specific pre-defined criteria that are used in grading the methodological quality of each study. The following outlines the rationale for <u>not</u> giving credit for specific methodological principles for each therapeutic study:

	Rationale for not giving credit
North	
Complete follow-up of ≥ 80%	<u>NO</u>: 75% follow-up (45/60) The primary outcome ("success") data was based on 45 (19 SCS + 26 reoperation) of the 60 patients randomized: In the results section, the authors wrote: "Among patients available for long-term follow-up, SCS was significantly more successful than reporation: 9 (47%) of 19 patients randomized to SCS and 3 (12%) of 26 patients randomized to reoperation achieved ["success"]…"
Controlling for possible confounding	<u>NO:</u> There was no table or detailed information of the baseline characteristics between the randomized groups (SCS vs reoperation). The study only provided the baseline characteristics of patients that refused randomization vs those randomized vs those treated. No other info about baseline characteristics of SCS vs reoperation groups could be identified in the text. [For credit, Spectrum requires a robust description description of baseline characteristics between groups to determine whether baseline characteristics between groups were similar.]

Methodological quality of prognostic studies assessing factors associated with outcome following spinal cord stimulation.

Methodological principle	Burchiel 1995	Lamé 2009	North 1991	North 1996	Turner 2010	Van Eijs 2010
Study design Prospective cohort study Retrospective cohort study Case-control study Case series	✓	✓	✓	✓	✓	✓
Patients at similar point in the course of their disease or treatment	✓	✓	✓	✓	✓	✓
Patients followed long enough for outcomes to occur	✓	✓	✓	✓	✓	✓
Complete follow-up of ≥ 80%		✓	✓		✓	✓
Controlling for extraneous prognostic factors*	✓	✓	✓	✓		✓
Evidence class	**II**	**I**	**II**	**II**	**II**	**II**

* Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Appendix F. MORTALITY: COFFEY ET AL (2009)

We identified an additional study by Coffey et al (2009)[90] that compared mortality from all causes (including ischemic and neuropathic) among patients receiving intrathecal opioid pumps with those receiving SCS implantation (control group). This study did not meet our criteria for inclusion and is discussed in Appendix F. that compared mortality from all causes among patients receiving intrathecal opioid pumps with those receiving SCS implantation (control group). This study did not meet our criteria for inclusion or critical appraisal (see Table 3) for two reasons: (1) patient diagnosis was not reported- study likely included patients who were treated for ischemic pain (we required least 75% of patients in case series to be diagnosed with neuropathic pain); and (2) mortality rates were provided only up to one year following implantation (we required follow-up of at least five years for observational studies). The authors reported the following cumulative mortality rates: 0.011% at 3 days, 0.09% at 30 days, and 1.36% at one year following hospital discharge[90].

The following should be noted with respect to the reported mortality rates in Coffey et al: (1) the reason for SCS was not reported; therefore, it is likely that a good percentage of the patients included in these rates were being treated for ischemic pain, and these patients are more likely to have cardiovascular-related deaths than those being treated from neuropathic pain (the current technology assessment population of interest); (2) how this rate compares with a control group of patients with similar disease is not known; (3) the mortality rates were based on data available from the Medtronic Device Registration System and the Social Security Administration Death Master File. In general, administrative databases are not the best method to obtain safety data for a number of reasons: they may contain data collected as a by-product of an unrelated process, data collection is not necessarily standardized and may have been performed by hundreds of individuals at multiple locations, data are usually not checked for quality, records may be of inconsistent structure and length even within a database, and data may be missing[101, 102]. Further, these databases were not created for research purposes and typically do not have researcher input regarding the design or types of information collected[103].

Appendix G. CLINICAL PEER REVIEWERS

Reviewer	Areas of expertise
Hugh W. Allen, MD Section Head, Pain Medicine Virginia Mason Medical Center Seattle, Washington Department of Anesthesiology	• Invertentional pain management
Andrew Friedman, MD Virginia Mason Medical Center Seattle, Washington Physical Medicine and Rehabilitation	• Spine care • Pain management • Electrodiagnostic medicine