Washington State Health Care Authority

Spinal Cord Stimulation – Rereview

Final Evidence Report

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Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/about-hca/hta
shtap@hca.wa.gov

Spinal Cord Stimulation – Re-review

Provided by:

Aggregate Analytics, Inc.

Prepared by:

Andrea C. Skelly, PhD, MPH
Erika D. Brodt, BS
Mark Junge, BS
Dakota Riopelle, MPH
Shay Stabler-Morris, MSc
Asmaa Khariji Watson, PhD

Internal clinical, methods review: Roger Chou, MD
Clinical experts/peer review: Carl Noe, MD; Kim Mauer, MD

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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 (HCA). 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. The 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.

Aggregate Analytics, Inc. is a contract research organization whose team has over fifteen years of experience in performing health technology assessments, comparative effectiveness reviews, and systematic reviews for a variety of clients based on accepted methodologic standards for such research. AAI's mission is to assist healthcare professionals and organizations in the objective synthesis and generation of evidence to improve future healthcare delivery by providing timely, methodologically rigorous, transparent services and quality evidence synthesis products.

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Abbreviations

AE = Adverse event
CI = Confidence interval
CMM = Conventional medical management
Conv. = Conventional
CRPS = Complex Regional Pain Syndrome
EQ-5D = EuroQol 5-Dimension Questionnaire
EQ-VAS = EuroQol-visual analogue scale
FBSS = Failed back surgery syndrome
FDA = Food and Drug Administration
F/U = Follow-up
HF = High frequency
Hz = Hertz
ICER = Incremental cost effectiveness ratio
KQ = Key question
KHz= Kilohertz
MCS = Mental component score
MD = Mean difference
MME = Morphine milligram equivalents
N/A = Not available/applicable
NPRS/NRS = Numerical pain rating scale/Numerical rating scale
NR = Not reported
NRSI = Nonrandomized study of interventions
NSRBP = Nonsurgical radicular back pain
ODI = Oswestry Disability Questionnaire
OR = Odds ratio
PCS = Physical component score
PDN = Painful Diabetic Neuropathy
PL = Profile likelihood
PT = Physical therapy
QALY = Quality-adjusted life year
QHES = The Quality of Health Economic Studies
QoL = Quality of life
RCT = Randomized controlled trial
ROB = Risk of Bias
RR = Risk ratio
SAE = Serious adverse event
SCS = Spinal cord stimulation
SD = Standard deviation

SE = Standard error
SF-12 = Short form-12 questionnaire
SF-36 = Short form-36 questionnaire
SOE = Strength of evidence
SR = Systematic review
U.S. = United States
VAS = Visual analog scales
WTP = Willingness to pay

Executive Summary

Introduction

Chronic pain is a leading cause of disability and is an immense public health challenge. Pain is chronic when it occurs for extended periods (usually defined as >3 months). Chronic pain affects other aspects of an individual's health and function, including physical, emotional, social, and mental, often leading to a loss in quality of life.[8,14,41,78,104,105] Treatment of chronic pain aims to improve function and quality of life in addition to pain relief. Primary treatments include disease and injury-specific treatments such as nerve root decompression or reoperation in patients with lumbar radiculopathy, and other therapies such as pharmaceuticals, physical therapy, behavioral and psychological therapies, and transcutaneous nerve electrical stimulation (TENS). Spinal cord stimulation (SCS) may be considered for moderate or severe pain that does not respond to standard therapies. A 2020 U.S. Food and Drug Administration (FDA) communication estimated that 50,000 SCS devices are implanted annually.[30] SCS was developed in the 1960's based on the Melzack and Wall's gate-control theory and has been used to treat a number of chronic pain issues, especially neuropathic pain.[64,87] Mechanisms of pain relief using SCS are not completely understood, although current theories suggest stimulation occurs through a pulse delivering a specific current to dorsal fibers which interfere with or suppress the transmission of pain signals between nerves and the brain.[43,65,86] Further details on the mechanism of SCS systems have been described in great detail elsewhere.[11,65,86]

SCS systems involve percutaneous implantation of electrode leads into the epidural space adjacent to the dorsal column of the spinal cord. Currently, 16 FDA approved SCS devices are available. Approved musculoskeletal indications generally include Failed Back Surgery Syndrome (FBSS), Complex regional pain syndrome (CRPS) Types I and II, intractable low back pain and leg pain. Other indications include epidural fibrosis, degenerative disc disease, and arachnoiditis. Some SCS devices are approved for treatment of diabetic neuropathy. In 2016 the FDA gave premarket approval (PMA) to the first generation of devices implanted onto the dorsal root ganglion (DRG) of the posterior root to treat CRPS type I or type II, reflex sympathetic dystrophy and causalgia.[28,29,95] Compared with SCS devices, in which leads are implanted into the epidural space, DRG leads enter the epidural space, exit the neuroforamina, and stimulate the adjacent DRG, potentially providing more focused pain relief through specific targeting, as well as decreased paresthesia.[19,65]

The SCS device has three parameters that can be adjusted to tailor the needs to the patient: the frequency, pulse width and pulse amplitude. The pulse frequency used in SCS, measured in hertz (Hz), can be adjusted to meet the needs of individual pain thresholds.[65,86] Traditional SCS systems are considered "low-frequency", typically defined as 30 Hz to 200 Hz, but may be as low as 10 Hz or high as 1200 Hz.[86] Low-frequency SCS is often associated with paresthesia, a feeling of tingling or buzzing that is perceived differently depending on the individual, which may or may not bring discomfort. "High frequency" (also referred to as "paresthesia free") SCS systems, often defined as greater than 200 Hz, produce stimulations that are typically unperceivable by patients, and may be preferred.[15] Currently, the highest frequency available is 10,000 Hz. Additionally, in 2016 the FDA approved a clinician application for SCS systems that provide stimulation in "bursts" rather than constant rates (referred to as burst stimulation), which may provide greater relief at lower frequencies.[16,25,50,66] Tonic stimulation occurs when a consistent pulse stream of a set amplitude, frequency and pulse width are delivered whereas groups of pulses at a lower amplitude and higher frequency are delivered during burst stimulation.[93]

Policy Context/Reason for Selection

A Health Technology Assessment (HTA) on SCS was performed in 2010 and reviewed by the Washington Health Technology Assessment Program (HTAP). The prior report focused on evidence for the effectiveness of and complications for traditional SCS (dorsal column) in patients with chronic neuropathic pain. Signal updates were performed in 2014, 2016, and 2018, all of which concluded that there was not substantial, high-quality new evidence comparing SCS with medical or surgical interventions that did not involve neuromodulation (e.g., SCS, DRG stimulators, peripheral nerve neuromodulation) to trigger an updated report. The HTAP is interested in re-evaluation of spinal cord stimulation as additional evidence on technical advances related to use of SCSs, including use of high frequency and burst stimulation, may be available. Dorsal root ganglion stimulators will not be included in this review, given differences in lead placement compared with traditional SCS. This is consistent with the scope of the prior report. The proposed assessment update will be restricted to devices approved by the FDA for management of the FDA-approved conditions related to neuropathic and non-neuropathic musculoskeletal pain as described in the PICOTS (Table A).

The draft Key Questions and Scope were published on the HTAP website from April 20 through May 3, 2023. Public comments to this posting draft, those related to topic nomination, and a petition sent to the HCA were reviewed and discussed with the HTAP. None led to changes in the questions or scope following consultation with the HTA Program. All citations suggested by commenters were evaluated for inclusion based on the final key questions and scope.

Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the effectiveness and safety of SCS for treatment of pain related to failed back surgery syndrome (FBSS), chronic back pain, complex regional pain syndrome (CRPS), or peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia) in adult patients not previously treated with SCS. The differential effectiveness and safety of these therapies for subpopulations will be evaluated, as will the cost effectiveness.

Key Questions and Scope

When used in adult patients who have failed other treatment options for pain related to FBSS, chronic back pain, CRPS, or peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia):

1. What is the evidence of short and long-term effectiveness of SCS compared with medical and/or surgical treatment (appropriate to condition) that does not include neuromodulation devices?
2. What is the evidence of the safety of SCS compared with medical and/or surgical treatment (appropriate to condition) that does not include neuromodulation devices?
3. What is the evidence that SCS has differential efficacy or safety issues in sub-populations of interest?
4. What is the evidence of cost-effectiveness of SCS compared with other medical or surgical options that do not include neuromodulation?

Table A. PICOTS/Scope:

Study Component	Inclusion	Exclusion
Population	Adults with one of the following: • chronic low back pain, failed back surgery syndrome* with low back pain and significant radicular pain, complex regional pain syndrome, peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia) Special populations/factors of interest: Sex, age, psychological or psychosocial co-morbidities, diagnosis or pain type, provider type, setting or other provider characteristics, health care system type, including worker's compensation, Medicaid, state, employees	• Children, patients <18 years old • Patients with prior use of SCS • Patients who are pregnant • All other pain conditions (e.g., cancer pain, chronic refractory anginal pain, heart failure, critical limb ischemia, peripheral vascular pain, pain at end of life, MS, fibromyalgia, headache, trigeminal neuralgia, chronic pancreatitis, chronic pelvic pain, chronic abdominal pain, post-stroke pain • Studies in which <75% of patients have chronic musculoskeletal or neuropathic pain or other included pain conditions and results for patients with these conditions are not reported separately
Intervention	FDA-approved spinal cord stimulation (permanently implanted pulse generator systems and radiofrequency receiver systems)	• Temporarily implanted spinal cord stimulation devices • Neurostimulation of other parts of the nervous system (e.g., peripheral nerves, deep brain), dorsal root ganglion stimulation • Transcutaneous electrical nerve stimulation (TENS) • Non-FDA approved devices (unless final, phase III trial) • Intrathecal pumps
Comparator	Medical and/or surgical treatment (appropriate to condition) that does not include comparison of SCS methods/devices or other neuromodulation devices	• Comparisons of SCS devices • Comparison of SCS combined with other interventions vs. the other intervention alone • Comparisons of different types/modalities of SCS (e.g., comparisons of low versus high frequency, burst vs. tonic, etc.)
Outcomes	**Primary Outcomes (SOE)** • Function • Pain • Opioid use • Complications and adverse effects (e.g., procedural complications and technical failures, harms, infection, revision, removal, painful paresthesia or loss of paresthesia, mortality, serious adverse events) **Secondary outcomes (No SOE)** • Health-related quality of life (HR-QoL) • Anxiety and depression • Patient satisfaction	• Non-clinical outcomes • Non-validated measures • Intermediate outcomes • Return to work

Study Component	Inclusion	Exclusion
	• Global perceived effect (GPE)/global impression of change	
Setting	Any	
Study design	• RCTs will be the primary focus; prospective high quality comparative nonrandomized studies of intervention (NRSI) with concurrent controls that control for confounding will be considered if RCTs are not available; question 3 is limited to RCTs • NRSIs including case series designed to evaluate harms with at least 5 years follow-up, or which report on rare harms for question 2 • Formal cost-effectiveness analyses assessing initial placement and replacement will be considered for question 4	• Case reports • Case series (for KQ1, 3, 4) • Case series not designed to evaluate harms, those with < 5 years follow-up for question 2 unless they report on rare harms outcomes • Non-clinical studies (e.g., animal studies) • Studies with N <10 patients total or <10 per group • Studies not reporting on primary outcomes or harms
Publication	• Studies published in English in peer reviewed journals, published HTAs or publicly available FDA reports • Full formal economic analyses (e.g., cost-utility analyses) published in English in an HTA, or in a peer-reviewed journal published after those represented in previous HTAs	• Abstracts, editorials, letters, books, conference proceedings • Studies without abstracts available online • 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/publications • Other types of economic evaluations (e.g., costing studies, cost-minimization analyses, cost-benefit analyses)

DRGS = Dorsal Root Ganglion Stimulation; FDA = Food and Drug Administration; GPE = Global perceived effect; HFSCS = High-frequency spinal cord stimulation; HR-QoL = Health-related quality of life; HTA = Health Technology Assessment; MS = multiple sclerosis; NRSI = Nonrandomized studies of interventions; RCT = Randomized Control Trial; SCS = Spinal cord stimulator; SOE = Strength of Evidence; TENS = Transcutaneous electrical nerve stimulation.
* Definitions of FBSS vary across studies.

Methods

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought during report development on specific clinical questions and to confirm outcomes on which to focus. The DRAFT report was posted for public comments. All comments were reviewed and suggested citations were evaluated for inclusion based on the final KQ and PICOTS criteria

listed above. Comments from clinical peer reviewers were received as were comments from internal clinical and peer review. All comments were reviewed and considered for preparation of the final report.

A formal, structured systematic search of the peer-reviewed literature was performed across multiple databases including PubMed and EMBASE to identify relevant peer reviewed literature as well as other sources (e.g., ECRI Guideline Trust) to identify pertinent clinical guidelines and previously performed assessments. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews. Studies were selected for inclusion based on pre-specified criteria detailed in the full report.

All records were screened by two independent reviewers; discrepancies were resolved by consensus. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria.

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria[106] based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[38] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[1] For parallel group RCTs criteria include adequate methods for randomization, allocation concealment, blinding, baseline comparability between study arms and completeness of follow-up. Additional potential sources of bias unique to crossover trials were evaluated based on Cochrane methods. Such sources include evaluation of group comparability after the first phase/period, incorporation of a sufficiently long washout period, mitigation of carryover effects and/or testing for carryover effects, use of correlated data analyses. For comparative NRSIs, patient sampling/inclusion methods, baseline comparability between treatment groups and control for confounding were assessed. Case series were considered at high risk of bias and not individually assessed. (Appendix E). In keeping with the AHRQ methods, each study was given a final rating of "good", "fair", or "poor" quality as described below. Discrepancies in ratings between reviewers were resolved through discussion and consensus. Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. in conjunction with consideration of epidemiologic principles that may impact findings.[72]

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[5,33,34] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[1] The SOE was based on the highest quality evidence available for the primary outcomes. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias.
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head-to-head).
- **Precision:** describes the level of certainty surrounding the effect estimates. It considers the variability around effect estimates and the extent to which a clinically useful conclusion may be possible.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias for outcomes related to benefits due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies and in the absence of a registered study protocol.[7,85] Publication bias could not reliably be assessed across studies using graphical or statistical tests for small sample effects, therefore this domain was eliminated from the SOE tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- **High –** Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- **Moderate –** Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable, but some doubt remains.
- **Low –** Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- **Insufficient –** We are unable to estimate an effect, have no confidence in the effect estimate for this outcome or the body of evidence has unacceptable efficiencies precluding judgment; Instances where all studies of a specific outcome were considered poor were rated as insufficient. Instances where there was no evidence were marked as such.

Reporting of magnitude of effect was based on the system used in many AHRQ pain reports (Appendix J).[13,89,90] For crossover trials, comparison between treatment groups following the first treatment period is preferable; none of the included crossover trials reported data for the first period, however. Methods for quantitative analysis are described in the full report. Briefly, meta-analyses were conducted using profile likelihood methods and focused on the primary outcomes. To determine the appropriateness of meta-analysis, clinical and methodological diversity were assessed as was statistical heterogeneity. Sensitivity analyses were considered excluding poor-quality trials, outlying data and related to clinical heterogeneity to the extent that data permitted.

Results

Out of a total of 1,551 unique citations identified from electronic database searches, hand searching and bibliography review of included studies, together with 10 studies carried over from the prior report, 49 studies – 13 RCTs (in 22 publications),[2,10,17,23,37,44,46-48,52,54,55,61,68,70,75-77,81,92,94,102] five comparative NRSIs (2 prospective and 3 retrospective)[22,59,74,100,107] and 30 single-arm (case series),[6,12,24,31,35,39,45,51,56,57,60,63,67,71,80,83,84,99,101,103,108] database[3,26,27,36,42,58] or registry[9,18,79] studies for safety – were included in this re-review which evaluated the efficacy/effectiveness and/or safety of spinal cord stimulation (SCS). Of the RCTs, four were crossover[2,37,52,94] and nine (in 18 publications) were parallel-group RCTs[10,17,23,44,46-48,54,55,61,68,70,75-77,81,92,102]. Most trials (69%) were funded by industry. In addition, eight formal cost-effectiveness analyses were included, two in U.S. settings and six in non-U.S. settings.[4,20,40,49,53,73,82,91]

Key Question (KQ) 1:

FBSS, Chronic Back Pain

SCS vs. Sham/Placebo – Crossover Trials, Key Points:

Three crossover RCTs (N=98 randomized) were identified that met inclusion criteria that compared SCS with sham/placebo stimulation for treatment of FBSS[2,94] and chronic radiculopathy after surgery for degenerative lumbar spine disorders[37] (Table B). Criteria for diagnosis or definitions of FBSS were not provided by trials.

- Similar results were seen for burst SCS and sham/placebo phases on measures of back or leg pain (VAS 0-10) or function (ODI 0-100) in one good-quality crossover RCT of 2 phases, 12-week phases per intervention in patients with chronic radiculopathy after low back surgery. (SOE: Moderate for back pain and function, Low for leg pain).
- Evidence was considered insufficient from two crossover trials (1 fair and 1 poor quality), evaluating individual SCS frequencies and SCS stimulation modalities versus sham/placebo in patients with FBSS.

Table B. Summary of evidence SCS versus sham/placebo stimulation from crossover trials in persons with chronic radiculopathy following back surgery or FBSS

Measure	SCS type(s)	≤3 months	>3 to <12 months	≥12 months
Chronic radiculopathy				
Function: ODI (0-100)	Burst	No evidence	Similar, 1 RCT (N=50) SOE: Moderate	No evidence
VAS back pain (0-10)	Burst	No evidence	Similar, 1 RCT (N=50) SOE: Moderate	No evidence
VAS leg pain (0-10)	Burst	No evidence	Similar, 1 RCT (N=50) SOE: Low	No evidence
FBSS				
Function (any measure)	Various frequencies	No evidence	No evidence	No evidence

VAS back pain (0-10)	1200 Hz 3030 Hz 5882 Hz	1 RCT, (N=24) SOE: Insufficient	No evidence	No evidence
VAS leg pain (0-10)	1200 Hz 3030 Hz 5882 Hz	1 RCT (N=24) SOE: Insufficient	No evidence	No evidence
VAS pain, NOS (0-10)	1000 Hz LF tonic Cluster tonic	1 RCT (N=18) SOE: Insufficient	No evidence	No evidence

Results favor SCS unless otherwise noted.
FBSS = failed back surgery syndrome, Hz = Hertz; LF = Low frequency; NOS = not otherwise specified; ODI = Oswestry Disability Index; RCT = randomized controlled trial; SOE = strength of evidence; VAS = Visual analogue scale.

SCS vs. CMM and vs. Reoperation – Parallel Trials, Key Points:

SCS vs. CMM

Three fair-quality RCTs (in 5 publications) (total N=477 randomized; N range, 100 to 218)[44,54,55,61,81] and four NRSIs, two prospective comparative NRSIs (total N=391 enrolled, N range 85 to 158[74,100] and two retrospective propensity-matched database studies (total N=253,603 matched, N range 7,560 to 246,043),[22,107] compared SCS with CMM (or usual care and pain clinic in one NRSI) for the treatment of FBSS (2 RCT, all 4 NRSIs) or nonsurgical refractory back pain (NSRBP) (1 RCT).[44] Criteria for diagnosis or definitions of FBSS were not provided by trials. The RCTs provide the primary evidence base for SOE (Table C).

- Overall, SCS was associated with significantly better outcomes compared with CMM up to 6 months (prior to crossover) in patients with chronic back pain; HF (10 kHz) SCS showed large effects while conventional SCS effects were more variable.
- In patients with FBBS with radiculopathy treated with conventional SCS versus CMM (2 fair-quality RCTs):
    - SCS was associated with large increases in the likelihood of achieving back and/or leg pain response (≥50% on VAS/NPRS) in both RCTs. Results according to pain scores were more variable but showed a moderate improvement with SCS versus CMM by 6 months across both trials (SOE: Low for all).
    - SCS was associated with a small improvement in ODI function scores at 6 months across both trials; no trial reported function responders (SOE: Low).
    - Evidence was considered insufficient across both trials to draw conclusions regarding opioid use.
- In patients with NSRBP treated with HF (10 kHz) SCS versus CMM (1 fair-quality RCT):
    - SCS was associated with a large increase in the likelihood of achieving back pain response (≥50% on VAS/NPRS) and function response (≥10-point reduction on ODI) at 3 and 6 months and a large improvement in back pain (3 and 6 months) and function (6 months) scores (SOE: Low for all).
    - Evidence was considered insufficient to draw conclusions regarding opioid use.

Table C. Summary of evidence SCS versus CMM from parallel trials in persons with chronic FBSS or NSRBP

Measure	3 months	6 months	≥12 months
FBSS with radiculopathy,* Conventional SCS			
LBP Responders (≥50% on VAS/NPRS)	No evidence	Large increase, 1 RCT (N=218) SOE: Low	No evidence
Leg Pain Responders (≥50% on VAS/NPRS)	Large increase, 1 RCT (N=94) SOE: Low	Large increase, 2 RCTs (N=312) SOE: Low	No evidence
LBP pain scores (VAS/NPRS, 0-10)	Small, 1 RCT (N=94) SOE: Low	Moderate, 2 RCTs (N=312) SOE: Low	No evidence
Leg pain scores (VAS/NPRS, 0-10)	Large, 1 RCT (N=94) SOE: Low	Moderate, 2 RCTs (N=312) SOE: Low	No evidence
Function Responders (≥10-pt. reduction, ODI)	No evidence	No evidence	No evidence
Function scores (ODI, 0-100)	No evidence	Small, 2 RCTs (N=312) SOE: Low	No evidence
Proportion of patients still using opioids	No evidence	Small decrease, 2 RCTs (N=290) SOE: Low	No evidence
Opioid use: mean MME dose	No evidence	2 RCTs (N=312) SOE: Insufficient	No evidence
NSRBP, HF (10 kHz) SCS			
LBP Responders (≥50% on VAS/NPRS)	Large increase, 1 RCT (N=159) SOE: Low	Large increase, 1 RCT (N=140) SOE: Low	No evidence
Leg Pain Responders (≥50% on VAS/NPRS)	No evidence	No evidence	No evidence
LBP pain scores (VAS/NPRS, 0-10)	Large, 1 RCT (N=143) SOE: Low	Large, 1 RCT (N=140) SOE: Low	No evidence
Leg pain scores (VAS/NPRS, 0-10)	No evidence	No evidence	No evidence
Function Responders (≥10-pt. reduction, ODI)	Large, 1 RCT (N=143) SOE: Low	Large, 1 RCT (N=140) SOE: Low	No evidence
Function scores (ODI, 0-100)	No evidence	Large, 1 RCT (N=140) SOE: Low	No evidence
Proportion of patients who stopped or decreased opioids	No evidence	Large increase, 1 RCT (N=140) SOE: Low	No evidence
Opioid use: mean MME dose	No evidence	1 RCT (N=74) SOE: Insufficient	No evidence

Results favor SCS unless otherwise noted.
FBSS = Failed back surgery syndrome; LBP = Low back pain; NOS= not otherwise specified; NPRS = Numerical pain rating scale; ODI = Oswestry Disability Index; RCT = randomized controlled trial; SOE = strength of evidence; VAS = Visual analogue scale.
* One trial enrolled patients with leg pain greater than back pain (Kumar) and the other patients with back pain greater than leg pain (Rigoard).

SCS vs. Reoperation

Evidence from one small, fair-quality RCT (N=60)[70] comparing conventional SCS with reoperation was insufficient to draw conclusions (Table D).

Table D. Summary of evidence SCS versus Reoperation from parallel trials in persons with chronic FBSS

Measure	Mean 2.9 years
Treatment success (≥50% pain improvement and patient satisfaction)	1 RCT (N=45) SOE: Insufficient
Opioid use: Proportion taking a stable or decrease dose	1 RCT (N=45) SOE: Insufficient

RCT = Randomized control trial; SOE = Strength of evidence.

Complex Regional Pain Syndrome

SCS vs. Sham/Placebo – Crossover Trials, Key Points:

Evidence was considered insufficient from one poor-quality multicenter, crossover RCT (N=33 randomized)[52] of SCS versus sham conducted in patients with a confirmed diagnosis of CRPS (Table E).

Table E. Summary of evidence SCS versus sham/Placebo stimulation from crossover trials in persons with CRPS

Measure	SCS type(s)	≤3 months	>3 to <12 months	≥12 months
VAS pain (NOS) (0-10)	40 Hz 500 Hz 1200 Hz Burst SCS	1 RCT (SOE: Insufficient)	No evidence	No evidence
McGill NRS average pain (0-10)		1 RCT (SOE: Insufficient)	No evidence	No evidence

Hz = Hertz; NOS= not otherwise specified; NRS = Numerical rating scale; RCT= randomized controlled trial; SCS = Spinal cord stimulator; SOE=strength of evidence; VAS = Visual analogue scale.

SCS vs. CMM/PT – Parallel Trials, Key Points:

Two RCTs (in four publications) (N=104 randomized; N range 50 to 54)[10,46-48] compared SCS versus PT or CMM for the treatment of CRPS (Table F).

- Conventional SCS was associated with improvement in pain and function compared with PT through 24 months in one fair-quality trial, with greater magnitudes of effect seen at earlier timepoints (SOE: Low); at 60 months, the evidence was considered insufficient to draw conclusions (SOE: Insufficient).
- Evidence from one small, poor-quality RCT that compared HF (10 kHz) SCS versus CMM was considered insufficient to draw conclusions.

Table F. Summary of evidence SCS versus CMM/PT from parallel trials in persons with CRPS

Measure	3 months	6 months	12-24 months	60 months
Conventional SCS				
Pain scores (VAS/NRS, 0-10)	Large, 2 RCTs (N=85) SOE: Low	Large, 2 RCTs (N=85) SOE: Low	Moderate2 RCTs (N=82) SOE: Low	1 RCT (N=44) SOE: Insufficient
Function scores (ODI, 0-100)	Moderate 1 RCT (N=31) SOE: Low	Small, 1 RCT (N=31) SOE: Low	Small, 1 RCT (N=31) SOE: Low	No evidence
HF (10 kHz) SCS				
Pain scores (VAS/NRS, 0-10)	1 RCT (N=29) SOE: Insufficient	1 RCT (N=29) SOE: Insufficient	1 RCT (N=29) SOE: Insufficient	No evidence
Function scores (ODI, 0-100)	1 RCT (N=29) SOE: Insufficient	1 RCT (N=29) SOE: Insufficient	1 RCT (N=29) SOE: Insufficient	No evidence

Results favor SCS unless otherwise noted.

HF = High frequency; kHz = Kilohertz; NOS= not otherwise specified; NRS = Numerical rating scale; ODI = Oswestry Disability Index; RCT = randomized controlled trial; SOE = strength of evidence; VAS = Visual analogue scale.

Painful Diabetic Neuropathy

SCS vs. CMM – Parallel Trials, Key Points:

Three fair-quality RCTs (total N=312 randomized; N range, 36 to 216)[44,54,81] compared SCS with CMM for the treatment of PDN (Table G).

- Both conventional and HF (10 kHz) SCS were associated with large improvements in pain (both pain response and pain scores) compared with CMM alone through 6 months.
- Evidence on opioid use was lacking; one RCT that evaluated conventional SCS found that opioid use was similar between groups at 6 months.
- SOE was Low for all outcomes and timepoints for both SCS types.

Table G. Summary of evidence SCS versus CMM from parallel trials in persons with PDN

Measure	3 months	6 months	≥12 months
Conventional SCS			
LE Responders (≥50% on VAS/NPRS)	No evidence	Large increase, 2 RCTs (N=96) SOE: Low	No evidence
LE Pain scores (VAS/NPRS, 0-10)	Large, 1 RCT (N=36) SOE: Low	Large, 2 RCTs (N=96) SOE: Low	No evidence
Opioid use: Proportion of patients still taking opioid; MSQ II scores	No evidence	Similar, 1 RCT (N=60) SOE: Low	No evidence
HF (10 kHz) SCS			
LE Responders (≥50% on VAS/NPRS)	Large increase, 1 RCT (N=184) SOE: Low	Large increase, 1 RCT (N=184) SOE: Low	No evidence
LE Pain scores (VAS/NPRS, 0-10)	Large, 1 RCT (N=180) SOE: Low	Large, 1 RCT (N=180) SOE: Low	No evidence
Opioid use	No evidence	No evidence	No evidence

Results favor SCS unless otherwise noted.

NOS= not otherwise specified; NPRS = Numerical pain rating scale; RCT= randomized controlled trial; SOE=strength of evidence; VAS = Visual analogue scale.

Key Question (KQ) 2:

Across all study types, there was substantial heterogeneity regarding how adverse events (AEs) were categorized, described, and reported which likely contributes to the broad range of AEs and their frequencies described in this report, making synthesis of AEs the challenging. Severity of or implications for some events (e.g., infection, lead migration) were not consistently reported or categorized. In most studies, it was not clear whether patients could experience more than one event. Many diverse AEs were reported across included studies, particularly the NRSIs. Based on clinical expert input, we attempted to prioritize and synthesize across common important categories of device-related and biological events as well as utilization-related (e.g., hospitalization due to AEs) events based on how information was described in the studies. Misclassification is possible. None-the-less the information presented in this review serves as a reasonable overview of the most important reported events. Summary tables for arms from RCTs and included comparative NRSI are available in the full report. Case series, registries and database studies often included patients who had SCS for a variety of indications and findings were not reported separately by indication; in general, the populations were primarily of those having SCS for FBSS. The SOE tables in the full report (Section 5) provide details of the numbers and types of studies as well as sample sizes for the prioritized adverse events to include those related to removal or revision of device components and serious biological events. Summary tables across NRSIs and detailed data abstraction tables from all studies are available in Appendix F.

Harms from included RCTs with at least *low SOE*

- There was low SOE for the following outcomes reported in RCTs:
    - The frequency of any SCS related AE ranged from 12.4% to 17.6% within 6 months (2 RCTs, total N=215, N range 102 to 113) and from 24.1% to 32.1% between 12–24 months (3 RCTs, total N=403, N range 84 to 174) in parallel group RCTs and was reported as 18% in one crossover trial (N=50).
    - SCS-related AEs requiring surgery ranged from 11.8% to 16.7% at 6 months (total N=126, N range 24 to 102) and from 23.8% to 37.5% at 12–24 months (total N=108, N range 24 to 84) in two parallel group RCTs.
    - Withdrawal due to AEs for SCS and CMM were similar within six months of implant, however there is substantial imprecision in effect estimates.

Device related AEs across study designs with at least *low SOE*

The frequency of device-related events varies substantially across study types and type of event. For nonrandomized studies the focus is on studies with at least 100 patients.

- The frequency the following device-related events as summarized in individual studies varied substantially across study designs (SOE low for all):
    - Any IPG device explantation: 1.4% to 25.2%
    - Any IPG revision or replacement: 0.9% to 22%
    - IPG removal for infection (1% to 5%) or infection or dehiscence (2.5% to 4.8%)
    - IPG removal specifically described as due to inadequate pain relief, loss of efficacy, lack of efficacy, inadequate benefit: 0% to 20.3%
    - Any lead/electrode replacement or revision: 3.4% to 17.9% (after exclusion of one small trial)

  - Lead failure or migration (surgery not specified): 0.9% to 9.5%
  - Lead fracture or failure: 1.1% to 15.8%
  - IPG revision or removal due to IPG displacement or migration: 0.5% to 1.2%
  - Serious infection (deep, fatal, leading to revision, removal, or hospitalization): 1.4% to 6%; reported within 30 days: 0.9%
  - Unintentional durotomy 6% (3/50); CSF leak, dural tear 0.6% to 0.7%
- Neurologic injury across study designs (deficit, paralysis, intraspinal abscess): 0% to 4% (after exclusion of one small trial) (SOE Moderate)

Adverse events for which evidence was *insufficien*t to draw conclusions

- RCTs (parallel group and crossover)
  - Mortality
  - Any SCS-related AE requiring surgery long term (60 months)
  - Any serious SCS-related AE
  - Withdrawal due to AE (NOS)
  - Electrode dislocation or reconfiguration
  - Comfortable paresthesia, SCS parameter concerns (Pmax, pulse width)
- Across study designs (for NRSI, studies of >100 pts)
  - IPG removal due to malfunction
  - Allergic reaction or anaphylaxis
  - AE requiring hospitalization

Key Question (KQ) 3:

No studies meeting inclusion criteria were identified. There was insufficient data to conduct subgroup analyses or test for interaction.

Key Question (KQ) 4:

Three full economic studies included in the 2010 review and eight studies published after that review suggest that SCS may be cost-effective versus conventional medical care.

Three full economic studies were included in the prior 2010 HTA,[69,88,96] one of which was part of a 2009 NICE HTA[88]; only one was conducted in the U.S.[69] The prior report concluded that evidence from these studies suggest 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 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.

Eight full economic studies published subsequent to the prior report met the inclusion criteria.[4,20,40,49,53,73,82,91] Six studies were of fair or good quality (QHES ranges 81/100 to 94/100), with two rated as poor quality (QHES 60/100, 73/100). Six studies evaluated SCS cost-effectiveness for FBSS or back pain.[4,20,40,53,73,82] Two of these also evaluated cost-effectiveness for CPRS[20,53] as did another study.[49]

Only one study was in patients with PDN.[91] Two studies were United States based.[40,73] Five were industry sponsored. Clinical outcomes data in analyses were generally from small clinical studies. Studies cite the lack of high-quality comparative data, particularly for newer SCS modes (e.g., HF-SCS) and for long term outcomes. Many modeled time horizons that extended beyond available clinical data. While many studies followed accepted methods for full economic analysis based on the QHES, assumptions about and modeling of effectiveness and harms, particularly longer term were not well articulated or supported clinical data from methodologically rigorous clinical studies in most studies. The range of effectiveness and frequency of harms were not generally evaluated in sensitivity analyses thus the impact of these as drivers of cost-effectiveness is not clear.

Key Findings across new studies:

- **FBSS and back pain**
  - Two U.S. based studies, one in patients with FBSS and another in patients with nonsurgical refractory back pain (NSRBP) were included.
    - One good quality cost-effectiveness study[40] in a Worker's Compensation population with FBSS found that that SCS is not cost effective at commonly considered WRT thresholds of either $50,000 or $100,000 compared with usual care or referral to a dedicated pain clinic over a 24-month time horizon. The applicability of these findings to other populations is unclear. Authors note that fewer patients had a successful SCS trial (53%) in the prospective cohort compared with what may be reported in RCTs in other populations.
    - One poor quality CUA[73] in patients with NSRBP reported a base-case ICER for 10-kHz SCS therapy combined with CMM of -$2,236/QALY at 6 months, significantly below the willingness-to-pay threshold of $50,000/QALY compared with CMM alone. Modeling of adverse events was not well described. When a mean cost of $30,000 for reimbursement for initial SCS and procedure costs was modeled, an ICER of over $200,000 at 6 months and approximately $100,000 QALY at 12 months (estimated from author's figure) is suggested. Authors state that cost-effectiveness can be achieved within 2.1 years when these costs are included.
  - Four CUAs conducted outside of the U.S.[4,20,53,82] evaluated the cost effectiveness of SCS plus CMM with CMM alone in patients with FBSS. Three were of good quality, one was poor quality. The applicability of these studies to the US healthcare system is unclear.
    - All concluded that SCS + CMM was more cost-effective than CMM alone based on usual willingness to pay thresholds. One study also compared SCS with reoperation, reporting that SCS was more cost-effective.
    - Study limitations: modeling of time-horizons beyond available clinical data, unclear modeling of long-term benefits and complications. Not all included initial SCS trial or implantation procedure costs.
- **CRPS:** Three good quality CUAs[20,49,53] conducted outside of the U. S. compared SCS + CMM with CMM alone for treatment of CRPS. The applicability of these studies to the US healthcare system is unclear.
  - All concluded that SCS + CMM was more cost-effective than CMM alone based on usual willingness to pay thresholds.

  - Two modeled a 15-year time horizon, one modeled a 20-year horizon. All note a concern about the lack of high-quality long-term data on benefits, harms, and costs to support long-term modeling.
- **PDN**: One good quality CUA conducted in the Netherlands[91] compared SCS with best medical therapy for PDN. The applicability of this study to the US healthcare system is unclear.
  - SCS was not cost-effective over the short term due to the substantial initial costs of SCS although it was considered more effective. Cost-effectiveness was sensitive to baseline cost imbalances; the impact of imputing missing data was unclear.

Strength of Evidence Summaries

Detailed SOE tables, including reasons for downgrading, are found in section 5 of the report.

Considerations

Research published subsequent to the 2010 HTA now includes a broader evidence base on the effectiveness and safety of SCS for certain chronic pain conditions. Many newer studies compared different types, frequencies or modes of SCS delivery and did not meet the inclusion criteria established *a priori.* Regarding safety, large nonrandomized studies with long-term follow-up provide additional insight into uncommon events and the frequency of events at time frames beyond currently available data from RCTs. Although longer follow-up is now available in some RCTs, long-term *comparative* evidence from high quality, well-powered studies remain sparse.

Newer literature includes cross-over trials evaluating different frequencies and modes of SCS stimulation compared with sham/placebo settings. In addition, new parallel group RCTs that evaluated SCS with CMM were identified. Most trials of both types of trials were considered fair. The magnitude of effects for many primary outcomes varied by the control/comparison group. Studies comparing SCS with sham/placebo (all were crossover trials) generally reported smaller effects than studies comparing SCS with CMM (all were parallel group trials) where patients could not be blinded. Large effects observed for patient-reported outcomes in pain studies in general may in part be due to lack of patient blinding, expectation of benefit, the natural history of a condition and other non-specific effects as well as a given intervention.[21] Many of the effect large effect estimates for effectiveness outcomes were imprecise as evidenced by large confidence intervals, calling into question estimate stability.

Included crossover trials evaluating different SCS modes/frequencies with sham in patients with FBSS or persistent radiculopathy following spine surgery varied with regard to phase length of stimulation for various SCS modes and sham ranging from 2 weeks to 12 weeks. None included a washout period between phases. Given possible difference in patient response to any given phase/modality and unclear sustainability of effects from one phase to the next, the extent to which carryover may be a problem is unclear particularly in studies using shorter treatment phases. Although one trial[2] reported that treatment interaction term for carryover effect was not significant, the study may have been underpowered to detect this. While all crossover trials reported steps to keep patients blinded to treatment phases, it is possible that patients may have been aware of treatments as some frequencies may have produces some level of noticeable paresthesia (unpleasant tingling or sensation) while others

(e.g., higher frequencies) may not. The impact of possible carry-over effects and loss of patient blinding are unclear.

The inclusion criteria for the RCTs (Appendix G) generally required that patients had failed conventional medical management. Most studies indicated that prior to SCS trial, patients were evaluated by a multidisciplinary team and that psychological evaluation was part of patient selection. Patients with psychological comorbidities and substance use disorder were excluded in most studies. Studies did not provide detail regarding specific methods, tools, or thresholds for the screening process, however. Many clinical and psychological factors are important to consider for patient selection.[32,62,98] There does not appear to be clear consensus regarding specific measurement tools (e.g., specific psychological measures) or clinical thresholds for evaluation. Results from included studies are most likely applicable to patients who are evaluated in multidisciplinary settings who have responded positively to trial SCS and do not have psychological comorbidities or SUD.

Most included studies evaluated SCS for types of chronic low back pain, however there is heterogeneity in included populations. FBSS was listed as the indication for SCS in a majority of trials, however definitions or diagnostic criteria were not usually described. In the literature, the definition of FBSS varies.[97] In some definitions, it is restricted to people who have technically successful decompression surgery [i.e., the cause of impingement was removed] but the patient has persistent radiculopathy. Other definitions are less specific and include persistent LBP (radicular or not) after LBP surgery, and don't require the surgery to be technically successful. It is unclear to what extent variation in FBSS definitions resulted in heterogeneity in study populations. One observational study[100] and related economic analysis[40] in patients with FBSS was in a Workers' Compensation population. As noted in the report, patient characteristics between this population and a more general population may differ and the generalizability of these studies to other populations is unclear. Some included studies were in patients with Nonsurgical Refractory Back Pain (NSRBP)[44] described as chronic refractory axial low back pain with a neuropathic component but specific criteria were not provided. The population consisted of patients who were not considered to be surgical candidates based on presentation or underlying pathology (80%) or had declined surgery or were at moderate to high surgical risk (20%).

Consultation with clinical experts for this report suggest that it is unclear how comparable/applicable the SCS parameters and thresholds used in the included RCTs may be to usual clinical practice, that there is likely heterogeneity in what is used clinically, and that SCS delivery parameters are tailored to the patient's needs. Settings in one cross-over trial [2]were generated using a custom-made programmer used exclusively for clinical investigations which may limit applicability. Some public comments suggested that parameters in another trial may not be routinely used[37] and may be set below usual stimulation parameters. In general, across included studies, there was heterogeneity in SCS parameters used.

Participants in all studies were likely to have concurrent mediations and have had other therapies in addition to SCS, which varied across participants, study arms and studies. Concurrent therapies and medications were poorly reported in most studies. The components and intensity of CMM were not described in detail by studies and it is unclear how comparable groups were on the types and intensity of CMM received. The impact of these factors on effectiveness or safety outcomes is unknown.

Information on safety and adverse events was abstracted from RCTs and NRSIs. Both types of studies have strengths and limitations. RCTs may usually have standardized protocols for monitoring and

reporting AEs and are less likely to have confounding by indication. They may have been underpowered to detect AEs and/or not had sufficient length of follow-up to evaluate safety long term. NRSI (case series, cohort studies, administrative database studies, registry studies) may provide better insight into AEs over a longer period and on uncommon or rare events if sufficiently powered. They have higher potential risk for selection bias and confounding, however. Misclassification of treatment and outcomes is also possible in administrative data. These factors are important to consider when interpreting results across different study types.

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1 Appraisal

1.1 Background and Rationale

Chronic pain is a leading cause of disability and is an immense public health challenge. Pain is chronic when it occurs for extended periods (usually defined as >3 months). Chronic pain affects aspects of an individual's health and function, including physical, emotional, social, and mental, often leading to a loss in quality of life.[17,28,72,129,171,172] Treatment of chronic pain aims to improve function and quality of life in addition to pain relief. Primary treatments include disease and injury-specific treatments such as nerve root decompression or reoperation, and other therapies such as pharmaceuticals, physical therapy, behavioral and psychological therapies, and neurostimulation therapies such as transcutaneous nerve electrical stimulation. Spinal cord stimulation (SCS) may be considered for moderate or severe pain that does not respond to standard therapies.

SCS systems involve percutaneous implantation of electrode leads into the epidural space adjacent to the dorsal column of the spinal cord. Currently, 16 FDA approved SCS devices are available. Approved musculoskeletal indications generally include Failed Back Surgery Syndrome (FBSS), Complex regional pain syndrome (CRPS) Types I and II, and intractable low back pain and leg pain. Other indications include epidural fibrosis, degenerative disc disease, and arachnoiditis. Some SCS devices are approved for treatment of diabetic neuropathy.

A Health Technology Assessment (HTA) on SCS was performed in 2010 and reviewed by the Washington Health Technology Assessment Program (HTAP). Additional research and technological advances have occurred since the 2010 review prompting the need for an updated review.

1.2 Policy Context

A Health Technology Assessment (HTA) on SCS was performed in 2010 and reviewed by the Washington Health Technology Assessment Program (HTAP). The prior report focused on evidence for the effectiveness of and complications for traditional SCS (dorsal column) in patients with chronic neuropathic pain. Signal updates were performed in 2014, 2016, and 2018, all of which concluded that there was not substantial, high-quality new evidence comparing SCS with medical or surgical interventions that did not involve neuromodulation (e.g., SCS, DRG stimulators, peripheral nerve neuromodulation) to trigger an updated report. The HTAP is interested in re-evaluation of spinal cord stimulation as additional evidence on technical advances related to use of SCSs, including use of high frequency and burst stimulation, may be available. Dorsal root ganglion stimulators were not included in this review, given differences in lead placement compared with traditional SCS. This is consistent with the scope of the prior report. The proposed assessment update was restricted to devices approved by the FDA for management of the FDA-approved conditions related to neuropathic and non-neuropathic musculoskeletal pain as described in the PICOTS (Table 1). Comments from the public posting of the KQ and PICOTS and consultation with the HTAP were considered for finalization of the Key Questions and scope.

The draft Key Questions and Scope were published on the HTAP website from April 20 through May 2, 2023. Public comments to this posting, those related to topic nomination and a petition sent to the HCA

Petition were reviewed and discussed with the HTAP. None led to changes in the questions or scope following consultation with the HTA Program. All citations suggested by commenters were evaluated for inclusion based on the final key questions and scope.

1.3 Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the effectiveness and safety of SCS for treatment of pain related to failed back surgery syndrome (FBSS), chronic back pain, complex regional pain syndrome (CRPS), or peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia) in adult patients not previously treated with SCS. The differential effectiveness and safety of these therapies for subpopulations was evaluated, as was the cost effectiveness.

1.4 Key Questions

When used in adult patients who have failed other treatment options for pain related to FBSS, chronic back pain, CRPS, or peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia):

1. What is the evidence of short and long-term effectiveness of SCS compared with medical and/or surgical treatment (appropriate to condition) that does not include neuromodulation devices?
2. What is the evidence of the safety of SCS compared with medical and/or surgical treatment (appropriate to condition) that does not include neuromodulation devices?
3. What is the evidence that SCS has differential efficacy or safety issues in sub-populations of interest?
4. What is the evidence of cost-effectiveness of SCS compared with other medical or surgical options that do not include neuromodulation?

PICOTS/Scope:

Study Component	Inclusion	Exclusion
Population	Adults with one of the following: • chronic low back pain, failed back surgery syndrome* with low back pain and significant radicular pain, complex regional pain syndrome, peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia) Special populations/factors of interest: Sex, age, psychological or psychosocial co-morbidities, diagnosis or pain type, provider type, setting or other provider characteristics, health care system type,	• Children, patients <18 years old • Patients with prior use of SCS • Patients who are pregnant • All other pain conditions (e.g., cancer pain, chronic refractory anginal pain, heart failure, critical limb ischemia, peripheral vascular pain, pain at end of life, MS, fibromyalgia, headache, trigeminal neuralgia, chronic pancreatitis, chronic pelvic pain, chronic abdominal pain, post-stroke pain • Studies in which <75% of patients have chronic musculoskeletal or neuropathic pain or other included pain conditions and results for patients with these conditions are not reported separately

Study Component	Inclusion	Exclusion
	including worker's compensation, Medicaid, state, employees	•
Intervention	FDA-approved spinal cord stimulation (permanently implanted pulse generator systems and radiofrequency receiver systems)	• Temporarily implanted spinal cord stimulation devices • Neurostimulation of other parts of the nervous system (e.g., peripheral nerves, deep brain), dorsal root ganglion stimulation • Transcutaneous electrical nerve stimulation (TENS) • Non-FDA approved devices (unless final, phase III trial) • Intrathecal pumps
Comparator	Medical and/or surgical treatment (appropriate to condition) that does not include comparison of SCS methods/devices or other neuromodulation devices	• Comparisons of SCS devices • Comparison of SCS combined with other interventions vs. the other intervention alone • Comparisons of different types/modalities of SCS (e.g., comparisons of low versus high frequency, burst vs. tonic, etc.)
Outcomes	**Primary Outcomes (SOE)** • Function • Pain • Opioid use • Complications and adverse effects (e.g., procedural complications and technical failures, harms, infection, revision, removal, painful paresthesia or loss of paresthesia, mortality, serious adverse events) **Secondary outcomes (No SOE)** • Health-related quality of life (HR-QoL) • Anxiety and depression • Patient satisfaction • Global perceived effect (GPE)/global impression of change	• Non-clinical outcomes • Non-validated measures • Intermediate outcomes • Return to work
Setting	Any	
Study design	• RCTs will be the primary focus; prospective high quality comparative nonrandomized studies of intervention (NRSI) with concurrent controls that control for confounding will be considered if RCTs are not available; question 3 is limited to RCTs)	• Case reports • Case series (for KQ1, 3, 4) • Case series not designed to evaluate harms, those with < 5 years follow-up for question 2 unless they report on rare harms outcomes • Non-clinical studies (e.g., animal studies)

Study Component	Inclusion	Exclusion
	• NRSIs including case series designed to evaluate harms with at least 5 years follow-up, or which report on rare harms for question 2 • Formal cost-effectiveness analyses assessing initial placement and replacement will be considered for question 4	• Studies with N <10 patients total or <10 per group • Studies not reporting on primary outcomes or harms
Publication	• Studies published in English in peer reviewed journals, published HTAs or publicly available FDA reports • Full formal economic analyses (e.g., cost-utility analyses) published in English in an HTA, or in a peer-reviewed journal published after those represented in previous HTAs	• Abstracts, editorials, letters, books, conference proceedings • Studies without abstracts available online • 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/publications • Other types of economic evaluations (e.g., costing studies, cost-minimization analyses, cost-benefit analyses)

DRGS = Dorsal Root Ganglion Stimulation; FDA = Food and Drug Administration; GPE = Global perceived effect; HFSCS = High-frequency spinal cord stimulation; HR-QoL = Health-related quality of life; HTA = Health Technology Assessment; MS = multiple sclerosis; NRSI = Non-randomized studies of interventions; RCT = Randomized Control Trial; SCS = Spinal cord stimulator; SOE = Strength of Evidence; TENS = Transcutaneous electrical nerve stimulation.
*Definitions of FBSS across studies vary.

1.5 Outcomes Assessed

This review focuses on the following primary effectiveness outcomes: validated measures of pain and function and opioid use. We focus on serious treatment-related adverse events, i.e., treatment-related events that may be life-threatening or required medical intervention. Clinical input on prioritization of harms and adverse events was obtained and reflected in the reporting of these. We also report on cost-effectiveness measures from full economic analyses. Table 1 provides a list of validated primary outcomes measures used in this review. We used definitions for the magnitude of effect size consistent with prior AHRQ reviews for treatment of pain,[24,144,145] Appendix J.

Table 1. Outcome Measures Used in Included Studies

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
PRIMARY					
Pain Visual Analog Scale (VAS-pain) / Numeric pain scale (NPS) / Numeric Pain Rating Scale (NPRS)	Patient	Patients are asked to indicate on a scale line (100 mm in length) where they rate their pain level of the day. One variation of this measure includes changing the length of the line.	0 to variable maximum of 10 or 100 (total score)	The higher the score, the greater the pain. No pain: 0 to 4 mm Mild pain: 5 to 44 mm Moderate pain: 45 to 74 mm Severe pain: 74 to 100 mm	For CLBP, FBSS, PDN or CRPS: NR
Douleur Neuropathique 4 (DN4) Questionnaire[19]	Clinician	Screening tool, consists of 10 items. 7 items related to pain quality (i.e., sensory and pain descriptors), based on an interview with the patient (assesses how the pain feels to the patient); 3 items based on the clinical exam. Clinician assesses whether there is reduced sensation (hypoesthesia) to touch or pinprick and whether light brushing increases or causes pain (allodynia).	0-10	The higher the scores, the more suggestive of neuropathic pain. Score ≥4 is suggestive of neuropathic pain	NR
Oswestry Disability Scale (ODI)[50,51]	Patient	Questionnaire examines perceived level of disability in 10 everyday activities of daily living. The 6 statements are	0%-100%	The higher the score, the greater the disability 0% to 20%: minimal disability	In patients with low back pain (various pathologies)[27,77,108]: Range, 9.5 to 12.9 points

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		scored from 0 to 5 and the final score is calculated as a percentage of the total points possible.		21%-40%: moderate disability 41%-60%: severe disability 61%-80%: crippled 81%-100%: bed bound	
SECONDARY					
EuroQol 5-Dimension Questionnaire (EQ5D)[49]	Patient	5 dimensions of health: Mobility Self-care Usual activities Pain/discomfort Anxiety depression Each dimension is rated on a scale from 1 (no problems) to 3 (extreme problems)	A 5-digit number is produced to represent level of problems in each dimension.	The higher the digit for each dimension, the greater the problems.	For CLBP, FBSS, PDN or CRPS: NR
EuroQol Visual Analog Scale (EQ-VAS)[2,49]	Patient	One item, asks the individual to select a number from a scale indicating their health state of the day.	0 to 100 (total score)	The higher the score, the lower the health impairment.	For CLBP, FBSS, PDN or CRPS: NR
Short Form-36 (SF-36)[178]	Patient	8 subscales (36 items): Role-functioning Role limitations due to physical health problems Bodily pain General health Vitality Social functioning Role limitations due to emotional problems Mental health The Mental Component Score	0 to 100 (subscale score) 0 to 100 (component score) Total score not used	The higher the score, the greater the quality of life.	For CLBP, FBSS, PDN or CRPS: NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		of the SF-36 (MCS-36) contains the subscales listed as 4-8 and includes 35 items. The Physical Component Score of the SF-36 (PCS-36) contains the subscales listed as 1-5 and includes 35 items.			
Short Form-12 (SF-12)[178]	Patient	A shorter version of the SF-36. 8 subscales (12 items): Physical functioning Role-physical Bodily pain General health Vitality Social functioning Role-emotional Mental health	0 to 100 (total score)	The higher the score, the lower the disability.	For patients with low back pain[38]: SF-12-MCS: 3.77 SF-12-PCS: 3.29

CLBP = Chronic low back pain; CRPS = Complex regional pain syndrome; DN4 = Douleur Neuropathique 4 Questionnaire; EQ5D = EuroQol 5-Dimension Questionnaire; EQ-VAS = EuroQol Visual Analog Scale; FBSS = Failed back surgery syndrome; MCID = Minimal clinically important difference; MCS = Mental Component Score; NPS = Numerical Pain Scale; NPRS = Numeric Pain Rating Scale; ODI = Oswestry Disability Index; PCS = Physical Component Score; PDN = Painful diabetic neuropathy; SF-12 = Short Form 12; SF-36 = Short Form 36; VAS = Visual analogue scale.
*MCIDs were only found if an outcome was significant in any of the results of this report. Those that are significant in the results, but not found searching the literature, then the MCID is reported as NR.

1.6 Washington State Utilization Data

2 Background

2.1 The Condition: Chronic Pain and Neuropathic Pain

The 2020 updated International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage".[75] The IASP emphasizes that pain is always a personal experience that it is influenced to varying degrees by biological, psychological and social factors. 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.[112] 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.[179]

Neuropathic pain has traditionally been defined by the IASP as pain resulting from a primary lesion or dysfunction in the central or peripheral nervous system.[74] 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.[8,107] Pain may be spontaneous or continuous.[129] 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.[11,156] 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.[11] A history of nervous system injury and a neuroanatomically plausible distribution of the pain is necessary.[163] Underlying causes may include infection, trauma, compression of nerves, and surgery. An associated lesion may or may not be identifiable,[44] however it is necessary to demonstrate a lesion or disease involving the nervous system using neurophysiological tests, imaging or biopsy to identify neuropathic pain.[163] Spontaneous pain can be manifested in neuropathic pain patients by stimuli which do not normally induce pain (termed "allodynia"),[8] 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")[8] such as hot or cold temperature.[44] Neuropathic pain patients commonly experience a marked loss in quality of life.[129] Chronic neuropathic pain is likely underdiagnosed and undertreated, and its estimated prevalence has been reported to range from 6.9% to 10%.[170] Neuropathic pain may be underdiagnosed; reported frequencies from epidemiologic studies range from 16% to 63%.[15]

Peripheral neuropathy encompasses a wide range of conditions that involve peripheral nervous system damage. Symptomatology depends on the types of nerves (e.g., sensory, motor or autonomic) that are involved. Acquired peripheral neuropathy causes may include conditions like diabetes, physical injury and infections that involve nerve tissue.[112] Diagnoses of peripheral neuropathic pain include complex regional pain syndrome (CRPS), carpal tunnel syndrome, painful diabetic neuropathy (PDN), 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 (note: these are out of scope for this review).[44] Patients with persistent back and/or leg pain following what appears to be successful spine surgery are diagnosed with failed back surgery syndrome (FBSS).[107] In the studies that met our inclusion criteria, the use of spinal cord stimulation was most evaluated in patients with FBSS (with leg pain meeting or exceeding back pain), followed by PDN and CRPS.

2.2 Chronic Low Back Pain

In the United States, low back pain contributes to 4.3 million years of disability annually—nearly double the impact of any other health condition.[113] Chronic low-back pain (CLBP), which affects around 13.1% of U.S. adults (one third of which endure moderate- to high-impact CLBP),[30,176] is associated with increased medical comorbidities, reduced productivity, and higher healthcare costs.[56,113]

Failed back surgery syndrome (FBSS) is a generalized disorder that is generally characterized by chronic pain in the lower back and/or legs that persists or recurs following anatomically successful spinal surgery.[76,168] There is no equivalent to FBSS following other types of surgery.[8] The term FBSS is controversial and has been variably applied and defined in the literature.[25,105,159] The term does not clearly separate out whether symptoms persist due to failure of the surgery to resolve the underlying issue or if they are a direct result of the surgery itself[105] and thus may not adequately describe causation.[25] Definitions and diagnostic criteria for FBSS were not described in most studies included in this review. Treatment of FBSS patients is difficult, as further surgery and conservative therapies typically do not relieve pain.[168] FBSS has been estimated to affect approximately 30% of patients following lumbar spine surgery, though reported estimates range from 10 to 40%.[76,92,119]

The term Nonsurgical Refractory Back Pain (NSRBP) has been used in included studies[78] for this report and was described as chronic refractory axial low back pain with a neuropathic component. The population consisted of patients who were not considered to be surgical candidates based on presentation or underlying pathology (80%) or had declined surgery or were at moderate to high surgical risk (20%) based on spine surgeon evaluation prior to randomization.

2.3 Painful Diabetic Neuropathy (PDN)

Painful diabetic neuropathy (PDN) is a distressing and often debilitating complication that arises from long-term uncontrolled diabetes. According to the Center for Disease Control's (CDC) *National Diabetes Statistics report* for 2022, 37.2 million Americans (11.3% of the U.S. population) have diabetes, with an estimated 23% of them undiagnosed.[22] Around 50% of people with diabetes are estimated to have peripheral neuropathy, and up to 25% will develop PDN.[81,149] This condition involves nerve damage, primarily affecting the peripheral nerves, and is characterized by intense and persistent pain. Individuals with PDN commonly experience burning, stabbing, or shooting sensations, along with heightened sensitivity to touch and temperature changes.[12,158] This neuropathic pain often begins in the extremities, such as the feet and hands, and gradually spreads, potentially impacting various aspects of daily life.[26,29,35,42] Managing PDN can be challenging, requiring a comprehensive approach that includes optimizing blood sugar control, medication, and various pain management strategies to enhance the individual's quality of life and alleviate suffering.

2.4 Complex Regional Pain Syndrome (CRPS)

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy or causalgia, is a neuropathic pain disorder that affects one or more limbs. Although 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.[132,150] 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.[150] CRPS tends to affect younger patients (mean age ranging from 36 to 46 years) and is more common in women.[138,150] In addition, the upper limb tends to be affected more commonly than the lower limb.[138] The estimated prevalence of CRPS type I is 20.57 per 100,000, and the incidence is 5.46 per 100,000 person years at risk, while the estimated prevalence and incidence of CRPS type II are 0.82 and 4.2 per 100,000.[138] Recent analyses of patient databases estimate prevalence at between 0.7% to 1.2%.[48,109,157]

2.5 The Technology: Spinal Cord Stimulation

Spinal cord stimulation (SCS) is usually not considered as a treatment for chronic pain until conventional therapies have failed to provide adequate pain relief. It is typically used in addition to other therapies for pain (e.g., conventional medical management or surgical options) 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. Given the complex relationship between clinical and psychological factors in chronic pain and its management, recommendations for patient selection have been proposed to help assure success with SCS. Such recommendations include multidisciplinary assessment, psychological and physical evaluation. There does not appear to be consensus regarding specific measurement tools (e.g., psychological measures) or clinical thresholds for aspects of these evaluations and many clinical and psychological factors are important to consider for patient selection.[57,100,160] Centers for Medicare Services (CMS) and other payers generally require this for reimbursement. Common specific requirements by payers include: SCS only as a late option after more conversative treatments have failed, careful screening, evaluation and diagnosis by a multidisciplinary team, appropriate psychological screening, no active substance abuse issues, and permanent implantation only after ≥50% pain reduction during a SCS trial period.

2.5.1 History and Mechanism of Action

SCS was first developed over fifty years ago by Shealy et al[142] based on Melzack and Wall's gate-control theory.[103] 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.[71,153]

Early use of SCS, 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 precise mechanism underlying the pain-relieving effects of SCS is not fully understood.[54] 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 proposed that SCS inhibits pain by acting on segmental spinal levels.[104] Possible mechanisms of action may include the enhancement of GABA (gamma-aminobutyric acid) and adenosine release 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; the inhibition of the excitatory amino acids glutamate and aspartate; and possibly an increase in the release of serotonin and substance P and peripheral blood flow.[104,153] Furthermore, MRI studies in humans showed that SCS triggered activity in the somatosensory cortex and the cingulated gyri, which are linked to processing the sensory and affective components of pain.[153] Additionally, most experts agree that the tingling and vibratory sensations of paresthesia, which occur with dorsal column stimulation, may mask the perception of pain. Successful pain reduction is dependent on complete overlap of the paresthesia with the painful region.[71] Further research is necessary to fully understand the mode of action by which SCS inhibits neuropathic pain.

In recent years, innovations in SCS systems have allowed the pulse frequency, measured in hertz (Hz), to be adjusted in order to address individual pain thresholds.[106,140] Traditional SCS systems, which are still the most widely used, deliver low frequency tonic stimulation.[92,119] Low frequency is typically defined as 30 Hz to 200 Hz, but may be as low as 10 Hz or capable of reaching as high as 1200 Hz.[140] Low frequency SCS often produces paresthesia, a feeling of tingling or buzzing which, depending on individual perception and preference, may or may not bring discomfort.[173] High frequency SCS systems, which can currently reach up to 10,000 Hz, produce stimulations that are unperceivable by patients, and may be preferable.[31,79,80,174] Additionally, in 2016 the FDA approved the use of SCS systems that stimulate in bursts, opposed to the traditional tonic systems.[114] Burst stimulation can potentially eliminate paresthesia at lower frequencies.[32,45,87]

2.5.2 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-controlled 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-to-14-day trial stimulation to determine whether they can achieve adequate pain relief as well as tolerate the paresthesia 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.[83,92,119,153] Trial stimulation involves implantation of the percutaneous electrode lead into the epidural space adjacent to 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,[83] while FBSS patients may have electrodes implanted in the T8-T10 levels of the spinal cord.[153] 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.[153] 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 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.[153] 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,[153] due to component failures or lead position.

2.5.3 Indications for use[4,16,18,101,115,136]

In the U.S., 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 for some devices, CRPS, radicular pain syndrome or radiculopathies, post-laminectomy pain, unsuccessful disc surgery, degenerative disc disease or herniated disc pain refractory to conservative and surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, and multiple back surgeries. Recently, some SCS systems have been approved by the FDA for use in patients with PDN. Each potential patient should undergo a period of trial stimulation before having an SCS device permanently implanted. We identified six manufacturers with FDA-approval for SCS devices; the devices currently listed on their company websites are below in Table 2.

Table 2. Current FDA-approved devices

Manufacturer FDA Number (year)	Device Name	Details	Indications	Contraindications
Boston Scientific PMA: P030017 (2004)	Precision Montage™ Precision™ Plus, Precision Spectra™ Precision Novi™ Spectra WaveWriter™ WaveWriter Alpha™	Rate: 2 to 1200 Hz Pulse width: 20 to 1000 µsec Amplitude: 0 to 25.5 mA	Management of chronic intractable pain of the trunk and/or limbs including unilateral or bilateral pain associated with the following: FBSS; CRPS Types I and II; intractable low back pain and leg pain, painful diabetic neuropathy.	Patients unable to operate the SCS system; have failed trial stimulation by failing to receive effective pain relief; are poor surgical risks; are pregnant
Medtronic PMA: P840001 (1984)	Vanta™ Intellis™ Itrel™ Synergy Versitrel™ Restore™ Family of Neurostimulators*	Frequency: 40-1000 Hz Pulse width: NR Amplitude: NR	Management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain, pain resulting from peripheral neuropathy.	Diathermy.
	PrimeAdvanced™ SureScan™ MRI	Rate: 2 to 130 Hz Pulse width: 60 to 450 µsec Amplitude: 0 to 10.5 mA	FBSS or low back syndrome or failed back; radicular pain syndrome or radiculopathies resulting in pain secondary to FBSS or herniated disk; Post laminectomy pain; Multiple back operations; unsuccessful disk surgery; degenerative disk disease; herniated disk pain refractory to conservative and surgical interventions; peripheral causalgia; epidural fibrosis; arachnoiditis or lumbar adhesive arachnoiditis; CRPS, reflex sympathetic dystrophy, or causalgia, pain resulting from peripheral neuropathy.	Diathermy.

Manufacturer FDA Number (year)	Device Name	Details	Indications	Contraindications
Saluda Medical PMA: P190002 (2022)	Evoke™ SCS system	Rate: 10 to 1500 Hz Pulse width: 20 to 1000 µsec Amplitude: 1 to 50 mA	Manage chronic pain in the trunk or limbs, including one-sided or two-sided pain associated with FBSS; intractable low back pain, or leg pain.	Cannot operate the SCS system; have not received effective pain relief during trial stimulation; are poor SCS surgical candidates.
Nevro Corp PMA: P130022 (2015)	Senza™ Senza™ II Omnia™	Rate: 1200 to 10000 Hz Pulse width: 40 µsec Amplitude 0.5 to 3.5 mA	Management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS; intractable low back pain, or leg pain. When programmed to include a frequency of 10000 Hz, are indicated as aids in the management of chronic intractable pain of the lower limbs, including unilateral or bilateral pain, associated with diabetic neuropathy.	Poor surgical candidates, including those with poor glycemic control in whom the safety of the device has not yet been characterized; fail to receive effective pain relief during trial stimulation; unable to operate the SCS system.
Abbott† PMA: P010032 (2001)	Proclaim™ XR Proclaim™ Plus Prodigy™ MRI Eterna™ Eon™ EonC™ Eon™ Mini	Rate: 2 to 1200 Hz Pulse width: 20 to 1000 µsec Amplitude: 0 to 25.5 mA	Management of chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS and intractable low back, or leg pain, diabetic neuropathy.	Unable to operate the SCS system; failed to receive pain relief during trial stimulation.
Biotronik PMA: P210037 (2023)	Prospera™	Rate: 2 to 1400 Hz Pulse width: 30 to 1000 µsec Amplitude: up to 20 mA	Failed back syndrome or low back syndrome or failed back; radicular pain syndrome or radiculopathies resulting in pain secondary to failed back syndrome or herniated disk; post-laminectomy pain;	Unable to operate the SCS system; failed to receive effective pain relief during SCS trial stimulation; patients who are poor SCS candidates based on presentation and underlying pathology.

Manufacturer FDA Number (year)	Device Name	Details	Indications	Contraindications
			multiple back operations; unsuccessful disk surgery; degenerative disk disease or herniated disk pain refractory to conservative and surgical interventions; peripheral causalgia; epidural fibrosis; arachnoiditis or lumbar adhesive arachnoiditis; CRPS; reflex sympathetic dystrophy, or causalgia.	

CRPS = Complex Regional Pain Syndrome; ECAP = Evoked Compound Action Potentials; FBSS = Failed Back Surgery Syndrome; FDA = Food and Drug Administration; Hz = hertz; mA = milliamp; MRI = Magnetic resonance imaging; NR = Not reported; PMA = Premarket approval; SCS = spinal cord stimulator; µsec = microsecond.
* Includes RestoreUltra™, SureScan™ MRI, RestoreSensor™ SureScan™, RestoreAdvanced™ SureScan™ MRI. Some of these devices have been recalled due to issues with the battery and software.
† Formerly St. Judes Medical.

2.5.4 Contraindications[4,16,18,54,101,115,136,165]

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,
- have infection at the surgical site,
- have abnormal anatomy that would preclude safe placement,
- have uncontrolled bleeding or coagulopathy.

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.[18,101]

2.6 Comparator Treatments

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.[150,156,168]

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.

Treatment for neuropathic pain is multidimensional and patient specific. Therapies may include the following[44,112]

Disease-specific interventions such as nerve root decompression or reoperation.

Pharmacological management may include opioid analgesics, non-steroidal 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 controlled trials. 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.

2.7 Published Clinical Guidelines

PubMed and EMBASE databases were searched for clinical guidelines regarding SCS using the same criteria and key words as the general literature search (Appendix B) with a focus on finding guidelines published or updated since the prior (2010) review. A total of nine guidelines fitting these criteria were identified. In addition to the guidelines listed below, clinical guidelines that were contained in the prior review are found in Appendix H.

Guidelines from the following sources are summarized (Table 3):

- American Society of Regional Anesthesia and Pain Medicine
- Dutch Quality of Healthcare Institute
- European Academy of Neurology
- Dutch Orthopedic Association and the Dutch Neurosurgical Society
- American Society of Interventional Pain Physicians
- Neuropathic Pain Special Interest Group
- Canadian Pain Society
- Neuromodulation Access Therapy Coalition
- National Institute for Health and Care Excellence

Table 3. Summary of Clinical Guidelines

Guideline	Year	Evidence Base	Recommendation	Rating/Strength of Recommendation
American Society of Regional Anesthesia and Pain Medicine	2023	NR	• In patients with chronic low back pain and/or leg pain, limb ischemia due to peripheral vascular disease, painful diabetic neuropathy, and/or CRPS type I or II a trial of SCS should be performed prior to a definitive SCS implant.	• Moderate (US Preventative Services Task Force rating)
Dutch Quality of Healthcare Institute	2022	NR	• Given the high initial costs and the invasiveness, the scientific committee has followed the general rule that primarily more conservative therapies should be used to treat the complaints. If there is insufficient effect and/or if relevant, too many side effects, neurostimulation can be advised. • **FBSS**: In the case of insufficient effect on conservative treatments, minimally invasive treatment can be considered. Treatment with epidural injections with local anesthesia and possibly corticosteroids in a PSPS (FBSS) in which there is scar pain can be considered. In a PSPS (FBSS) in which the neuropathic and/or nociplastic pain is prominent, a pulsed radio frequency of a nerve root can be considered.	NR

			• **CRPS**: Based on the available literature, combined with the expert opinion, the Scientific Committee recommends considering the following conservative treatments before applying neurostimulation. In the case of insufficient effect on conservative treatments, minimally invasive treatment can be considered. In upper extremity CRPS where vasomotor dysregulation is prominent, a thoracic block(T2–3) with local anesthetic and corticosteroids can be considered. In a residual CRPS situation in which neuropathic and/or nociplastic pain is prominent, a low dose of intravenous ketamine therapy can be considered. • **PDPN**: Based on the available literature, combined with the expert opinion, the Scientific Committee recommends considering conservative treatments before applying neurostimulation. In the case of insufficient effect of conservative treatments, minimally invasive treatment can be considered. Transcutaneous electrical nerve stimulation can be considered for a PDPN in which pain is the main focus. In the case of a PDPN in which vasomotor	

			dysregulation is prominent, a sympathetic blockade can be considered.	
European Academy of Neurology	2016	• **Post-surgical chronic leg and back pain (CBLP)**: Spinal cord stimulation added to conventional medical management versus conventional management alone or versus reoperation in post-surgical CBLP: 2 RCTs • **CRPS and PDN**: Spinal cord stimulation added to conventional medical management versus conventional management alone in CRPS and PDN: 2 or 3 RCTs	• **CBLP**: There is weak recommendation for the use of SCS added to conventional medical management versus conventional medical management and for the use of SCS as an alternative to reoperation in post-surgical CBLP • **CRPS and PDN**: There is weak recommendation for the use of SCS added to conventional medical management versus conventional medical management in PDN and CRPS I	• **CBLP**: Moderate (GRADE) • **CRPS and PDN**: Low (GRADE)
Dutch Orthopedic Association and the Dutch Neurosurgical Society	2015	• 2 RCTs	• FBSS: Neuromodulation is recommended for patients with FBSS who have pronounced leg pain and for whom conservative therapy has provided insufficient or no effect.	• **FBSS**: Based on the lack of a scientific conclusion and these other considerations, the task force developed the following positive recommendation for practice (because effectiveness is demonstrated in various RCTs, and the benefits clearly outweigh the risks and burdens)
American Society of Interventional Pain Physicians	2013	• 2 RCTS, 12 NRSIs	• **FBSS**: SCS is indicated in chronic low back pain with low-er extremity pain secondary to FBBS, after exhausting multiple conservative and interventional modalities.	• **FBSS**: The evidence is fair for spinal cord stimulation (SCS) in managing patients with failed back surgery syndrome (FBSS)

Neuropathic Pain Special Interest Group	2013	• **FBSS**: 2 RCTs • **CRPS type I**: 1 RCT, 1 SR, 1 Guideline • **CRPS type II**: NR • **PDN**: 1 NRSI	• **FBSS**: SCS is effective in treating FBSS • **CRPS type I**: SCS is effective in treating CRPS type I • **CRPS type II**: Very limited evidence • **PDN:** Weak evidence with small, positive case series with large effects in refractory DPN over long-term follow-up	• **FBSS**: Quality of evidence: Moderate; Strength of recommendation: Weak • **CRPS type I**: Quality of evidence: Moderate; Strength of recommendation: Weak • **CRPS type II:** Quality of evidence: Low; Strength of recommendation: Inconclusive • **PDN**: Quality of evidence: Low; Strength of recommendation: Inconclusive
Canadian Pain Society	2012	• 2 RCTs, 1 SR, 1 Guideline	• **FBSS**: In patients with FBSS who are not candidates for corrective surgery and who have failed conservative therapy, a SCS trial should be considered • **CRPS**: In patients with CRPS who are not candidates for corrective surgery and who have failed conservative therapy, a SCS trial should be considered	• **FBSS**: Level of evidence: Good; Rating of recommendation: B • **CRPS**: Level of evidence: Good; Rating of recommendation: B
Neuromodulation Access Therapy Coalition	2008 (Incorrectly noted in Deer, 2014)	• 8 RCTs	• SCS is effective in treating chronic neuropathic pain	NR
National Institute for Health and Care Excellence Technology appraisal guidance [TA159], Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin	2008 (Original) 2014 Re-review	• 11 RCTs (3 RCTs in people with neuropathic pain due to FBSS) • 8 RCTs in patients with ischaemic pain, 4 of which were for treatment of angina	• 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	• NR; no overall description of level of evidence in guideline document. • The Committee noted that only a small number of clinical trials had been identified and that relatively small numbers of people were included in these studies. The Committee

[2008 original assessment included in prior review] *See Table 5 for device-specific evaluations by NICE*			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.	accepted that there was some uncertainty about how the effects of pain treatments were sustained over time, but concluded that benefits could be sustained for at least up to 5 years in pain of neuropathic origin (for FBSS, CRPS)

			2014 Re-review Decision: The implementation section updated to clarify that spinal cord stimulation is recommended as an option for treating chronic pain of neuropathic or ischemic origin. Nothing new that affects the recommendations in this guidance was identified. This guidance will be reviewed if there is new evidence that is likely to change the recommendations.	

CLBP = Chronic lower back pain; CRPS = Complex regional pain syndrome; FBSS = Failed back surgery syndrome; NR = Not reported; NRSI = Non-randomized controlled trial of interventions; PDN = Painful diabetic neuropathy; RCT = Randomized control trial; SCS = Spinal cord stimulation; VAS = visual analog scale.

2.8 Previous Systematic Reviews & Health Technology Assessments

Recently published systematic reviews (SRs) and health technology assessments (HTA) included nine SRs[40,41,46,53,68,121,141,154,162] and four government reports.[65,110,111,123] Several reviews included mixed patient populations, and so their relevance is limited. Additionally, several reviews compared different SCS modalities, which is out of scope for this review. Lastly, some reviews did not differentiate between parallel and crossover trials.

Two large reviews were Cochrane reviews. Traeger 2023 was focused on back and leg pain and looked at SCS compared to placebo or CMM.[162] O'Connell also compared SCS to placebo or CMM, but did not differentiate between conditions, and studies included patients that had prior experience with SCS.[121] Each of these reviews separated parallel and crossover RCTs in their analyses. Additional recent systematic reviews of varying methodological quality are also briefly summarized. Further, there was overlap between included studies on patients in back pain across systematic reviews of this condition and there was overlap in studies across systematic reviews of other conditions. Systematic reviews summarized below may vary with regard to key questions and PICOTS scope compared with this re-review and results may differ. This update review focuses on the relevant primary studies meeting our inclusion/exclusion criteria.

Four government reports published since the prior report are summarized below. Two publications were from the National Institute for Health and Care Excellence (NICE): one report compared high-frequency (10 kHz) stimulation using the Senza™ SCS system versus conventional low-frequency SCS[111] and the other compared closed- versus open-loop spinal cord stimulation using the Evoke® system[110]. Both NICE publications are device-specific and both refer back to the original 2008 guidance listed in Table 3. A third report by the Ontario Health Technology Assessment (HTA) Series[123] compared high frequency SCS to either low frequency or burst SCS systems and briefly summarized the findings of each of the included RCTs, but did not synthesize data. The comparisons in all three of these reports were not within the scope of this review. A fourth report published by Haute Autorité de Santé (HAS) in France provides a summary of recommendations and an overview of literature assessed and process followed, but did not provide details about the type of SCS or the comparator treatments evaluated.[65] A related primary HTA or SR was not found.

Tables 4 and 5 summarize the previous SRs and HTAs/other government documents, respectively.

Table 4. Selected Previous Systematic Reviews*

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
SCS vs. placebo							
O'Connell 2021[121] Inception to September 2021 CENTRAL, MEDLINE Ovid, Web of Science, Health Technology Assessments, ClinicalTrials.gov, WHO International Clinical Trials Registry	To evaluate the efficacy, effectiveness, adverse events, and cost-effectiveness of implanted spinal neuromodulation interventions for people with chronic pain.	FBSS, Chronic limb or back pain, FNSS, Myelopathy, Myelomalacia, PDN, CRPS, Irritable bowel syndrome†	<u>Pain</u> VAS <u>Function</u> ODI, EQ-5D <u>Health-related QoL</u> EQ-5D, McGill Pain Questionnaire <u>Adverse events</u> infection, lead failure, re-operation‡	6 RCTs	Yes (Cochrane)	Yes	<u>Pain</u> Very low quality evidence (GRADE) from pooled analyses (crossover RCTs) showed a difference in VAS pain scores favoring SCS compared to placebo at short-term follow-up (timing NR; MD -8.73 (95% CI -15.67 to -1.78)). Stratified by SCS type, pooled analyses showed no difference for LF SCS (MD -7.88 (95% CI -28.14 to 12.38)), HF SCS (MD-4.31 (95% CI -10.29 to 1.67)), or burst SCS (MD -13.38 (-30.09 to 3.34)). <u>Function</u> Very low quality evidence (GRADE) from 1 crossover RCT showed a difference in function favoring SCS compared to placebo at short-term (timing NR; MD -7.48 (95% CI -13.13 to -

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							1.82)). Stratified by SCS type showed a difference in burst SCS [MD -10.30 (95% CI -18.48 to -2.12)) but not LF SCS (MD -4.90 (95% CI -12.72)] <u>Health-related QoL</u> Very low quality evidence (GRADE) from pooled analyses (crossover RCTs) showed no difference in QoL between SCS and placebo at short-term follow-up (timing NR; MD 0.03 (95% CI -0.30 to 0.35)). Stratified by SCS type showed no difference between LF SCS (1 RCT; MD 0.03 (95% CI -0.60 to 0.64)), burst SCS (1 RCT; MD -0.04 (95% CI -0.66 to 0.58)), or HF SCS (1 RCT; MD 0.07 (95% CI -0.41 to 0.55)) and placebo. <u>Adverse events</u> Only 1 crossover RCT reported AEs by group (GRADE: very low): 0%

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							infection, lead failure, or re-operation[‡]. Other crossover RCTs[§] reported incidence of lead failure (4 studies; 2-13%), infection (3 studies; 0-3%), and reoperation (3 studies; 3-39%).
Traeger 2023[162] Inception to June 10, 2022 CENTRAL, Medline, EMBASE, clinical trial registers	To assess the effects, including benefits and harms, of SCS for people with low back pain.	Low back pain, leg pain	<u>Pain</u> VAS <u>Function</u> Roland-Morris Disability Questionnaire, modified ODI[**] <u>QoL</u> EQ-5D <u>Adverse events</u> Withdrawal due to AE AE incidence Serious AE incidence	10 crossover RCTs	Yes (Cochrane)	Yes	<u>Pain</u> Low quality evidence (GRADE) from pooled analyses showed a difference in VAS back pain favoring LF SCS compared to placebo (MD -16.57 (95% CI -23.63 to -9.52)), but not HF SCS (MD -11.44 (95% CI -23.72 to 0.84)) or burst SCS (MD -13.53 (95% CI -32.61 to 5.56)) at immediate (1 month) follow-up. Overall pooled analyses favored SCS compared to placebo (MD -13.79 (95% CI -20.62 to -6.96)) at 1 month. Moderate quality evidence (GRADE) from 1 RCT showed no difference at medium (6

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							months) follow-up (MD -4.0 (95% CI -8.9 to 0.19)). Very low quality evidence (GRADE) from 1 RCT showed a difference in VAS leg pain favoring LF SCS compared to placebo (MD – 30.10 (95% CI -60.09 to -0.11)); pooled analyses did not show a difference between HF SCS and placebo (MD -3.83 (95% CI -15.61 to 7.95)) at immediate (1 month) follow-up. Overall pooled analyses showed no difference between SCS and placebo (MD -10.03 (95% CI -20.33 to 0.27)) at 1 month. Moderate quality evidence (GRADE) from 1 RCT showed no difference at medium (6 months) follow-up (MD -2.00 (95% CI -6.47 to 2.47)) <u>Function</u> Very low quality evidence (GRADE) from pooled

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							analyses showed no difference in function between SCS and placebo (MD -15.1 (95% CI -25.7 to 4.5)) at 1 month. Moderate quality evidence (GRADE) from 1 RCT showed no difference in function between SCS and placebo (MD -1.30 (95% CI -3.91 to 1.31) at medium-term (≥3 to <12 months)) follow-up. <u>QoL</u> Very low quality evidence (GRADE) showed no difference in health-related QoL between SCS and placebo at 1 month (1 RCT, MD 0.02 (95% CI -0.10 to 0.13) or ≥3 months (1 RCT, MD 0.04 (-0.08 to 0.16) <u>Adverse events</u> Withdrawals due to AEs: Very low quality evidence (GRADE) from 1 RCT found no difference between SCS

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							and placebo for withdrawals from AEs (n=2; details NR) AEs: Very low quality evidence (GRADE) from 1 RCT showed 18% (9/50) SCS patients experienced AEs by 12 months. Serious AEs: Very low quality evidence (GRADE) from 3 RCTs (not pooled) found 4.1%, 5.5%, and 8% of participants required surgical revision at 12 weeks, 8 weeks, and 12 months respectively.
Duarte 2021[41] Inception to May 2020 MEDLINE, CENTRAL, Embase	To identify and assess the effectiveness of SCS compared with usual care and other treatment alternatives for the management of PDN.	PDN	<u>Pain</u> VAS Pain ≥50 pain reduction <u>Health-related QoL</u> EQ-5D	2 RCTs	Yes (Cochrane)	Yes[††]	<u>Pain</u> Pooled analyses reported a difference in VAS pain scores favoring SCS compared to CMM at 6 months (MD -3.13 (95% CI -4.19 to -2.08)). GRADE not reported, both RCTs considered high risk of bias. Pooled analyses reported a difference in the proportion of patients with ≥50% pain

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							reduction favoring SCS compared to CMM at 6 months (RR 0.08 (95% CI 0.02 to 0.38)). GRADE not reported, both RCTs considered high risk of bias. <u>Health-related QoL</u> Pooled analyses reported a difference in EQ-5D utility index favoring SCS compared to CMM at 6 months (MD 0.16 (95% CI 0.02 to 0.30)). GRADE not reported, both RCTs considered high risk of bias. Pooled analyses reported a difference in EQ-5D self-reported health favoring SCS compared to CMM at 6 months (MD 11.21 (95% CI 2.26 to 20.16)).

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
Duarte 2022[40] Inception to December 2021 MEDLINE, CENTRAL, Embase, WikiStim	To evaluate the effectiveness of SCS for PDN.	PDN	<u>Pain</u> VAS NRS ≥50% reduction in pain <u>Health-related QoL</u> EQ-5D VAS EQ-5D index <u>Adverse events</u>	3 RCTs‡‡	Yes (Cochrane)	Yes	<u>Pain</u> Moderate quality evidence (GRADE) from pooled analyses showed a difference in pain favoring both LF SCS (2 RCTs; MD -3.83 (95% CI -4.76 to -2.90)) and HF SCS (1 RCT; MD -4.90 (95% CI -5.47 to -4.33)) compared to CMM at 3 months. This effect continued for LF SCS (MD -3.13 (2 RCTs; 95% CI -4.19 to -2.08)) and HF SCS (1 RCT; MD -5.20 (95% CI -5.77 to -4.63)) compared to CMM at 6 months. Very low quality evidence (GRADE) from pooled analyses showed a difference in the proportion of patients with ≥50% pain reduction favoring both LF SCS (2 RCTs; RR 12.69 (95% CI 2.61 to 61.73)) and HF SCS (1 RCT; RR 15.82 (95% CI

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							6.72 to 37.31)) compared to CMM at 6 months. <u>Health-related QoL</u> Low quality evidence (GRADE) from pooled analyses showed a difference in EQ-5D VAS for both LF SCS (2 RCTs; MD 11.21 (95% CI 2.26 to 20.16)) and HF SCS (1 RCT; MD 18.10 (95% CI 12.58 to 23.62)) compared to CMM at 6 months. Moderate quality evidence from pooled analyses showed a difference in EQ-5D index for both LF SCS (2 RCTs; MD 0.16 (95% CI 0.02 to 0.30)) and HF SCS (1 RCT; MD 0.17 (95% CI 0.12 to 0.21)) compared to CMM at 6 months. <u>Adverse events</u> One RCT (LF SCS vs. CMM) reported 1 infection, 2 cases

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							of incomplete paresthesia, 2 cases of pain due to the IPG, and 1 patient with coagulopathy complicating the procedure; all resolved and did not require explant. Another RCT (LF SCS vs. CMM) reported 1 patient developing a dural puncture followed by a lethal subdural hematoma, and 1 patient with infection that required explant. The third RCT (HF SCS vs. CMM) reported 2 treatment-related serious AEs (device extrusion and infection), and 18 other AEs in 14 patients with HF SCS; the most common being infection and wound dehiscence, with 2 patients required explant following infection.
SCS + CMM vs. CMM alone							

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
O'Connell 2021[121] Inception to September 2021 CENTRAL, MEDLINE Ovid, Web of Science, Health Technology Assessments, ClinicalTrials.gov, WHO International Clinical Trials Registry	To evaluate the efficacy, effectiveness, adverse events, and cost-effectiveness of implanted spinal neuromodulation interventions for people with chronic pain.	FBSS, Chronic limb or back pain, FNSS, Myelopathy, Myelomalacia, PDN, CRPS, Irritable bowel syndrome†	<u>Pain</u> VAS ≥50% pain relief <u>Function</u> ODI <u>Health-related QoL</u> ODI EQ-5D <u>Adverse events</u> Lead failure/replacement Infection Reimplantation <u>Opioid use</u> <u>Economic</u>	5 RCTs	Yes (Cochrane)	Yes	<u>Pain</u> Very low quality evidence (GRADE) from pooled analyses showed a difference in VAS pain score favoring SCS + other interventions compared to other interventions alone at short-term (timing NR; MD -37.41 (95% CI -46.39 to -28.42)), medium (timing NR; MD – 31.22 (95% CI -47.34 to -15.10)), but not long-term (MD -7.0 (95% CI -24.76 to 10.76)) follow-up. Very low quality evidence (GRADE) from pooled analyses showed a difference in proportion of patients reporting ≥50% pain relief at short (RR 15.90 (95% CI 6.70 to 37.73)), medium (RR 7.08 (95% CI 3.40 to 14.71)) and long-term (RR 15.15 (95% CI 2.11 to 108.91)) follow-up

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							Low to Very low quality evidence (GRADE) from pooled analyses showed a difference in the proportion of patients with ≥50% pain relief favoring SCS + CMM compared to CMM at short-term (timing NR; RR 15.90 (95% CI 6.70 to 37.73)) medium-term (timing NR; RR 7.08 (95% CI 3.40 to 14.71)) and long-term follow-up (timing NR; RR 15.15 (95% CI 2.11 to 108.91)). <u>Function</u> Very low quality evidence (GRADE) from pooled analyses showed no difference in function between SCS + CMM compared to CMM at short-term (timing NR; MD -15.93 (95% CI -35.99 to 4.13)), but did find a difference favoring SCS + CMM compared to CMM at medium-term

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							follow-up (timing NR; MD 0.73 (95% CI 0.46 to 0.99)). <u>Health-related QoL</u> Low to Very low quality evidence (GRADE) from pooled analyses reported a difference in QoL favoring SCS + other interventions compared to other interventions at medium follow-up (MD 0.73 (95% CI 0.46 to 0.99)). One RCT reported no difference in QoL at long-term follow-up (timing NR; MD -0.09 (95% CI -0.74 to 0.56)). <u>Adverse events</u> Very low quality evidence (GRADE) from pooled analyses reported the incidence of lead failure/displacement as 0.9% to 14% (RD 0.04 (95% CI -0.04 to 0.11)), infection as 3% to 7% (RD 0.04 (95% CI 0.01 to 0.07)),

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							reoperation/reimplantation as 2% to 31% (RD 0.11 (95% CI 0.02 to 0.21)) at medium follow-up (timing NR). One study reported long-term (5 years) incidence of lead failure/displacement at 55% (RD 0.55 (95% CI 0.35 to 75)) and reoperation/reimplantation at 94% (RD 0.94 (95% CI 0.80 to 1.07)). <u>Opioid use</u> Low quality evidence (GRADE) from pooled analyses showed no difference between SCS + other interventions compared to other interventions alone in opioid use at medium-term follow-up (timing NR; RR 0.77 (95% CI 0.58 to 1.01)). <u>Economic</u> One RCT reported unadjusted costs at 6

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							months to be €12653 (SD 2756) for SCS + CMM versus €2594 (SD 2939) for CMM alone (MD €10059 (95% CI 8742.39 to 11375.61)). Full cost-effectiveness not reported. Another RCT found societal costs to be €25539.20 for SCS and €5313.45 for CMM. From a societal perspective, there was an ICER of €94159.65 per QALY for SCS versus CMM, and from a healthcare perspective the ICER was €34518.85 per successfully treated patient.
Traeger 2023[162] Inception to June 10, 2022 CENTRAL, Medline, EMBASE, clinical trial registers	To assess the effects, including benefits and harms, of SCS for people with low back pain.	Low back pain Leg pain	<u>Pain</u> VAS <u>Function</u> Roland-Morris Disability Questionnaire Modified ODI[**] <u>QoL</u> EQ-5D	3 parallel RCTs	Yes (Cochrane)	Yes	<u>Pain</u> Low quality evidence (GRADE) from 1 RCT showed no difference in VAS back pain between SCS + CMM and CMM at short-term (3 months) follow-up (MD -8.70 (95% CI -18.95 to 1.55) Low quality evidence (GRADE) from pooled

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
			<u>Adverse events</u> Withdrawal due to AE AE incidence Serious AE incidence <u>Opioid use</u>				analyses showed a difference in VAS back pain scores favoring LF SCS + CMM (2 RCTs, MD -11.78 (95% CI –16.74 to -6.81)) and HF SCS + CMM (1 RCT, MD -54.6 (95% CI -61.03 to -48.17)) compared to CMM at medium-term follow-up (≥3 to <12 months). Overall pooled analyses showed no difference between SCS + CMM compared to CMM (MD -25.97 (95% CI -56.17 to 4.23)). Low quality evidence from 1 RCT a difference in VAS leg pain favoring SCS + CMM compared to CMM (MD -32.30 (95% CI -42.30 to -22.30)) at short term (3 months) follow-up. Very low quality evidence (GRADE) from pooled analyses showed a difference in VAS leg pain

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							favoring LF SCS + CMM compared to CMM (MD -18.84 (95% CI -33.21 to -4.47)) at medium (≤3 to <12 months) follow-up. <u>Function</u> Low quality evidence (GRADE) from 1 RCT showed a difference in function favoring SCS + CMM compared to CMM (MD -12.6 (95% CI -20.1 to -5.2)) at short-term (3 months) follow-up. Low quality evidence (GRADE) from pooled analyses showed a difference in function at medium-term (≥3 to <12 months) follow-up favoring SCS + CMM compared to CMM (MD -16.19 (95% CI -19.36 to -13.01)). When stratified by SCS type, 1 RCT (MD -28.8 (95% CI -33.81 to -23.79)), and 2 RCTs (MD -7.72 (95% CI -11.82 to -3.62)

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							showed a difference for HF SCS and LF SCS respectively. <u>QoL</u> Very low quality evidence (GRADE) showed no difference in health-related QoL between LF SCS + CMM and CMM (MD 7.63 (95% CI -0.61 to 15.87)) at medium-term (≥3 to <12 months) follow-up. <u>Adverse events</u> Withdrawal due to AEs: Very low quality evidence (GRADE) from 1 RCT showed no difference between SCS + CMM and CMM (n=2; details NR). AEs: Very low quality evidence (GRADE) from pooled analyses showed no difference between SCS + CMM and CMM (RR 2.32 (95% CI 0.39 to 13.79) at medium (≥3 to <12 months) follow-up. Stratified by SCS

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							type found a difference for HF SCS + CMM (RR5.77 (95% CI 2.34 to 14.20) but not LF SCS + CMM (RR 1.03 (95% CI 0.74 to 1.42)). One RCT only reported the incidence of specific AEs: lead migration (10%), lead/extension fracture (2%), IPG migration (1%), loss of therapeutic effect (1%), technique-related events (5%), infections (8%), pain at incision site (6%), neurostimulator pocket fluid collection (5%). Serious AEs: Very low quality evidence (GRADE) from 1 RCT showed no difference between HF SCS + CMM and CMM (RR 1.73 (95% CI 0.51 to 5.87)). <u>Opioid use</u> Low quality evidence (GRADE) from pooled analyses showed no difference in reduction in

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							opioid usage in SCS + CMM compared to CMM (RR 0.85 (95% CI 0.73 to 1.00) at medium-term (≥3 to <12 months) follow-up.
Mixed comparisons							
El Saban 2023[46] §§ Inception to May 31, 2022 MEDLINE, EMBASE, Epub, Ovid, Scopus	To synthesize evidence on physical function in SCS.	Chronic back pain	<u>Function</u> ODI	7 RCTs*** 4 NRSI 24 case series 1 sub analysis of RCT	Yes (Cochrane)	Yes†††	<u>Function</u> Very low quality evidence (GRADE) from pooled analyses showed a significant increase in function at 3 (MD -19.90 (95% CI -28.24 to -11.57)), 6 (MD -11.20 (95% CI -14.85 to -7.55)), 12 (MD -17.00 (95% CI -23.07 to -10.94)), and 24 (MD -17.11 (95% CI -20.88 to -13.34)) months.
Falowski 2023[53] Dates NR PubMed, MEDLINE, EMBASE, Google Scholar	Literature review of adverse events following SCS	NR	<u>Adverse events</u> Allergic reaction Infections Hematoma Dural puncture Lead migration Implant related pain	1 RCT 11 NRSI	No	No	<u>Adverse events</u> Overall rates of SCS related AEs are rare, though general complications may be more common. AEs may include allergic reaction (0.2%), infections (1-10%), hematoma & bleeding (<1%), dural puncture (<1-

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
			Spinal cord injury & neurological compromise				2%), lead migration (≤5%), implant related pain & discomfort (1-12%), spinal cord injury & neurological compromise (0.19-2.35%)
Ho 2022[68] Dates NR PubMed, EMBASE, CINHAL [study overlap with O'Connell, 2021]	To provide evidence for the use of SCS to treat CRPS and characterize the additional benefits of various SCS waveforms.	CRPS	<u>Pain</u> VAS GPE	4 RCTs‡‡‡	Yes (Cochrane)	Yes	<u>Pain</u> Low to high quality evidence (GRADE) showed a difference in VAS pain scores favoring LF SCS compared to CMM or placebo (Time point NR; MD -1.17 (95% CI -1.61 to -0.73)). High quality evidence (GRADE) showed a difference in GPE scores favoring LF SCS compared to CMM or placebo (time point NR; MD 1.58 (95% CI 1.00 to 2.15)).
Strand 2022[154] Dates NR Database NR	To explore the safety and effectiveness of treating PDN with neuromodulation.	PDN	<u>Adverse events</u> Migration or fracture Revision of leads or IPG IPG replacement Infection Explant	3 RCTs§§§ 4 case series	No	No	<u>Adverse events</u> AE rates across RCTs and NRSI were low at 6, 12, and ≥24 months, though sample sizes were small. The most common were lead migration or fracture (1-30%), revision of leads or

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							IPG (1-30%), IPG replacement (9-38%), infection (3-20%), and explant (2-17%).
Shanthanna 2023[141] Inception to March 2022 Medline, EMBASE, Cochrane	To synthesize evidence regarding patient selection and the SCS trials.	Chronic non-cancer pain	<u>Adverse events</u> Lead migrations Infection Pain at implant site Cerebrospinal fluid leak Reoperation	60 SRs 36 RCTs 41 NRSI	No	No	<u>Adverse events</u> SRs: Complications were generally reported as rare, with lead migrations (3-24%) and infections (1-11%) being the most common. Others include pain at implant site (3%), cerebrospinal fluid leak (7%), reoperation (15-24%), explants (1-20%). One case of paralysis, one death from subdural hematoma. Neurological complications rare (data NR). Anywhere from 0% to 81% had at least one complication. RCTs: Complications not reported often. Pain at implant site (6%), lead migration/fracture (2-17%), minor headache (2%),

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions
							infections (3-5%), headache (5%). NRSI: Complications not reported often. Lead migration (1%), infection (1-6%). Case reports: Major infections requiring surgical management were noted in 31% (4/13), spinal hematoma in 23% (3/13(, and epidural lipomatosis in 15% (2/13) of case reports. One case report assessed the influence of axial lead migration and the need to adjust stimulation in 24 patients during SCS trials.

AE = adverse event; CI = confidence interval; CMM = conventional medical management; CRPS = Complex regional pain syndrome; EQ-5D = EuroQol 5 Dimensions; FBSS = Failed Back Surgery Syndrome; FNSS = Failed Neck Surgery Syndrome; GPE = Global Perceived Effect; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HF = high frequency; ICER = incremental cost-effectiveness ratio; IPG = implantable pulse generator; LF = low frequency; MD = mean difference; NR = not reported; NRSI = non-randomized control of intervention; ODI = Oswestry Disability Index; PDN = painful diabetic neuropathy; QALY = quality adjusted life year; QoL = quality of life; RCT = randomized control trial; RD = risk difference; RR = risk ratio; SCS = spinal cord stimulation; SR = systematic review; VAS = visual analogue scale.

* Based on scope of this review, we did not include comparisons of different SCS modalities.

† Authors do not split analyses by diagnostic population.

‡ All patients in this RCT were recruited after experiencing stable pain relief from existing SCS, so this may explain no incidence of these AEs.

§ These crossover RCTs did not report AEs by study group.

** Modified ODI was transformed into a 0 to 100 scale.

†† Did not include outcomes that occurred following potential crossover at 6 months.

‡‡ Exclusion criteria included follow-up studies after crossover.

§§ Includes studies with patients receiving LF SCS, HF SCS, CMM + SCS, vs. SCS, CMM, as well as patients randomized by anatomic vs. paresthesia placement.

*** Included 2 crossover RCTs, but did not separate these from parallel RCTs or NRSI in the analyses.
††† Meta analyses included crossover RCTs, parallel RCTs, NRSI and case series.
‡‡‡ 2 studies compared SCS vs. CMM, 2 RCTs compare SCS vs. placebo. Additionally, 3 RCTs tested different frequencies or burst patterns, but not reported here. Two of the RCTs were crossover RCTs. Authors combined crossover and parallel RCTs in the meta-analyses.
§§§ Included SCS vs. CMM.

Table 5. Selected Previous Health Technology Assessments and other Government Reports

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
SCS (in general)							
Haute Autorite De Sante (HAS) 2014[65] Dates NR Database NR	To clarify indications for 3 categories of neurostimulator assessed by the National Committee for the Evaluation of Medical Devices and Health Technologies (CNEDiMTS): • Non-rechargeable neurostimulator with a maximum of 8 electrode leads (referred to below as a nonspecific neurostimulator) • Non-rechargeable neurostimulator with high-capacity cell and a maximum of 16 electrode leads (referred to below	FBSS, CRSP, critical limb ischemia (CLI)	Pain Oswestry Disability Index Patient satisfaction QoL Analgesic consumption Number of amputations Complications	2 health technology assessment reports and 3 clinical practice guidelines	NR – Authors note publications selected (HTAs, guidelines) were of good methodological quality, but the quality of the studies included was considered poor to moderate (limited numbers of patients, identified biases, lack of blinding)	No	Conclusions: • FBSS and CRPS: literature results in agreement, confirmed importance of SCS for these. • CLI: data didn't allow conclusions. • Indications for treatment vary across countries and reflect the low level of evidence for SCS. • CNEDiMTS considers that SCS has a role in treatment for: ○ chronic pain of neuropathic origin, after the failure of therapeutic alternatives, due to radicular or axial pain syndrome of diabetic, post-herpetic, traumatic

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
	as a specific neurostimulator). • Rechargeable neurostimulator with a battery and a maximum of 16 electrode leads.						or surgical origin persisting for at least one year ○ CRPS types I and II persisting for at least 6 months ○ Preimplantation assessment and successful trial (7days, ≥50% pain relief) required; information of risks, including those related to repeat surgery. • Lack of conclusive data comparing neurostimulators with each other; specific devices of no particular clinical importance vs. non-specific devices and no reason to distinguish between them.
LF SCS							
NICE 2020[110] * Dates NR Database NR	To summarize costs, efficacy, safety of the Evoke® SCS for chronic neuropathic or ischemic pain;	Chronic back and leg pain	<u>Pain</u> VAS ≥50% reduction in back and leg pain	1 RCT 1 Case series	No	No	<u>Main point</u>: The 2 studies show that Evoke® is more effective than open-loop spinal cord stimulation in

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
Device-specific summary, not a full technology review; the 2008 NICE guidance is referenced for SCS in general (Table 3)	Focus on comparing closed loop (Evoke) vs. Open loop (fixed output). Comparison is not in scope for this HTA		without increase in pain medication <u>Opioid use</u>				people with intractable back and leg pain. <u>Pain</u> RCT: 82% of close-loop patients experienced ≥50% reduction in pain compared to open-loop (60%) SCS patients at 3 months. At 12 months, this difference was sustained (83.1% vs. 61%). Case series: At 12 months, VAS reduced from mean 81.3 (SD 1.6) to 21 (SD 3.4). 81.4% reported a ≥50% reduction in pain. <u>Opioid use</u> RCT: 55% of close-loop SCS patients compared to 40% of open-loop SCS patients had reduced or eliminated opioid use. Case series: 84.9% of patients had reduced or eliminated opioid use by 12 months.

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
	Senza™						
HF SCS							
NICE 2019[111] *Device-specific summary, not a full technology review; the 2008 NICE guidance is referenced for general guidance on SCS (Table 3)* *Report reviewed July, 2022, no revision to guidance reported in August 2023.*	To assess the clinical and cost effectiveness of Senza™ SCS system for delivering HF10 therapy to treat chronic neuropathic pain. Focuses on comparison HF with conventional SCS (Comparison is not in scope for this HTA)	Chronic neuropathic back or leg pain after failed back surgery; New evidence in patients with diabetic neuropathy	Pain, function, opioid use	1 RCT 5 NRSIs Compares HF with conventional SCS.	NR	None reported.	2019 Guidance conclusion - Pain and function: HF 10 Devices is at least as effective as low-frequency SCS in reducing pain and functional disability, and avoids the experience of tingling sensations (paresthesia). Recommendation: HF10 therapy should be considered for patients with residual chronic neuropathic back or leg pain (at least 50 mm on a 0 mm to 100 mm visual analogue scale) at least 6 months after back surgery despite conventional medical management and who have had a successful trial of stimulation as part of a wider assessment by a

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
							multidisciplinary team. 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. **August 2023**: NICE reviewed the guidance and literature and found nothing new that affects the recommendations in this guidance. Author state that Patients with other causes of neuropathic pain were included in the evaluation and may be considered for HF10 therapy using Senza SCS but any additional benefits compared with low-frequency SCS are less certain.

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
Ontario HTA 2020[123] † Inception to August 2018 Medline, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment database, NHS EED	To assess safety and effectiveness of 10 kHz SCS for adults with chronic non-cancer pain that does not respond to medical management Focus: Comparison of HF vs. LF SCS; (Comparison is not in scope for this HTA)	Chronic non-cancer pain	Pain VAS Clinically significant difference in pain Function ODI Global impression of change Health related QoL SF-12 EQ-5D Patient satisfaction Adverse events Neurological deficits Stimulation-related AEs Major AEs Non-serious AEs Lead migration Wound complications	5 RCTs‡ 2 Economic analyses	Yes (Cochrane)	No	Pain Parallel RCTs: Moderate quality evidence (GRADE) from two RCTs found that HF SCS was superior to LF SCS at reducing VAS back and leg by ≥50% at 3, 6 and 24 months (Data not synthesized). 1 RCT did not find a difference between HF and LF SCS for VAS pain at 12 months. Crossover RCTs: Low quality evidence (GRADE) from two crossovers reported a difference in VAS back and leg pain from baseline for burst, LF, and HF SCS. Between group differences were not reported. Function Moderate quality evidence (GRADE) from 3 parallel RCTs reported no difference in improved function between HF SCS and LF SCS at 3, 6, 12, and

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
			Infections Implant site pain Dysfunction Surgical revision <u>Opioid use</u> <u>Economic</u>				24 months. Crossover RCTs did not report this outcome. <u>Global impression of change</u> Moderate quality evidence (GRADE) from 1 parallel RCT reported a difference in self-reported and physician rated change favoring HF SCS compared to LF SCS at 12 and 24 months (only proportions reported). Moderate quality evidence (GRADE) from another RCT reported no difference in patient or physician rated change at 3, 6, and 12 months. A third RCT reported that all patients demonstrated improvements, but did not report change scores for comparison groups. Crossover RCTs did not report this outcome.

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
							Health-related QoL Moderate quality evidence (GRADE) from 1 parallel RCT reported for the physical and mental health subscores favoring HF SCS compared to LF SCS at 12 months. Moderate quality evidence from another RCT reported no difference in physical or mental health subscores between HF and LF SCS at 6 or 12 months. A third RCT reported a significant difference in EQ5D from baseline for each group, but did not report between group differences (moderate quality evidence). Crossover RCTs did not report this outcome. Patient satisfaction Moderate quality evidence (GRADE) from 1 parallel RCT reported that 83% of HF SCS and 79% of LF SCS

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
							were satisfied or very satisfied at 12 months. This had increased at 24 months to 86% and 86% for HF and LF SCS respectively. Crossover RCTs did not report this outcome. <u>Adverse events</u> One RCT reported no stimulation-reported neurological deficits for either SCS group. Stimulation-related major AEs (not defined) occurred in 4% and 7% of HF and LF SCS patients respectively. The most common major AEs were lead migration (3% vs. 5%) and wound complications (4% vs. 3%). 1 patient in each HF and LF SCS group dies respectively. Non-serious AEs were more common and occurred in 28% versus 33% of patients, with the most common

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
							being implant site pain (12% vs. 10%). Another RCT reported no infection, neurological deficits, implant site pain, or dysfunctions for either SCS group. Surgical revision occurred in 3% versus 7% of patients. A third RCT reported that the only major AE was an infection that required hospitalization in a LF SCS patient. Overall AEs occurred in 22% versus 31% of HF and LF SCS patients, and revision in 11% of all patients. The most common AE was lead migration (16%). GRADE quality was not reported. Crossover RCTs did not report this outcome. <u>Opioid use</u> Low quality evidence (GRADE) from 1 parallel RCT reported that 36% of HF SCS and 26% of LF SCS

SR Search dates Database	Purpose	Condition	Primary Outcomes	Evidence Base	Risk of Bias Assessed (Tool)	Quantitative Synthesis	Primary Conclusions or Recommendations
							had reduced or eliminated opioid use by 12 month follow-up. Crossover RCTs did not report this outcome. <u>Economic</u> One analysis found that HF SCS, LF non-rechargeable SCS, and LF rechargeable SCS cost £87400, £95156, and £92196, respectively. ICER was not reported. Another study found that compared to CMM and reoperation, HF SCS had an ICER of £3153 and £2666 per QALY gained respectively.

AE = adverse event; CLI = critical limb ischemia; CMM = conventional medical management; CRPS = complex regional pain syndrome; EQ-5D = EuroQol 5 Dimensions; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HF = high frequency; HTA = Health Technology Assessment; ICER = incremental cost-effectiveness ratio; kHz = kilohertz; LF = low frequency; NICE = National Institute for Health and Care Excellence; NR = not reported; ODI = Oswestry Disability Index; QALY = quality adjusted life year; QoL = quality of life; RCT = randomized control trial; SCS = spinal cord stimulation; SD = standard deviation; SF-12 = 12 item Short-form survey; SR = systematic review; VAS = visual analogue scale.

* Includes Open loop vs closed loop comparison, which were not included in the current HTA.

† Authors did not synthesize data, but instead reported all relevant data for each individual study in detail. A few outcomes reported MDs (with very few confidence intervals), though most were reported as mean scores or mean within-group change from baseline.

‡ 3 parallel RCTs and 2 crossovers. Includes comparison of HF SCS to LF SCS or burst SCS.

2.9 Medicare and Representative Private Insurer Coverage Policies

Per vendor contract, summary of the Centers for Medicare Services (CMS) National Coverage Determination (NCD) and a minimum of two bellwether payer policies is provided below. This is not intended as a complete listing of payer policies or appraisal of policies**.**

Table 6. Summary of Payer Policies

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Centers for Medicare Services (CMS) NCD – Electrical Nerve Stimulators (160.7) Last review: 08/07/1995 Next review: NR	NR	NR	There are two types of implantations covered by this instruction: Dorsal Column (Spinal Cord) Neurostimulation - The surgical implantation of neurostimulator electrodes within the dura mater (endodural) or the percutaneous insertion of electrodes in the epidural space is covered. Depth Brain Neurostimulation - The stereotactic implantation of electrodes in the deep brain (e.g., thalamus and periaqueductal gray matter) is covered.	No payment may be made for the implantation of dorsal column or depth brain stimulators or services and supplies related to such implantation, unless all of the conditions listed below have been met: The implantation of the stimulator is used only as a late resort (if not a last resort) for patients with chronic intractable pain; With respect to item a, other treatment modalities (pharmacological, surgical, physical, or psychological therapies) have been tried and did not prove satisfactory, or are judged to be unsuitable or contraindicated for the given patient; Patients have undergone careful screening, evaluation

				and diagnosis by a multidisciplinary team prior to implantation. (Such screening must include psychological, as well as physical evaluation); All the facilities, equipment, and professional and support personnel required for the proper diagnosis, treatment training, and follow up of the patient (including that required to satisfy item c) must be available; and Demonstration of pain relief with a temporarily implanted electrode precedes permanent implantation.
Centers for Medicare Services (CMS) via Noridian Healthcare Solutions, Inc. LCD – Spinal Cord Stimulators for Chronic Pain (L36204)	NR	Yes	The implantation of spinal cord stimulators (SCS) may be covered as therapies for the relief of chronic intractable pain. SCS is best suited for neuropathic pain but may have some limited value in other types of nociceptive severe, intractable pain. Therapy consists of a short trial with a percutaneous implantation of neurostimulator electrode(s) in the epidural space for assessing a patient's suitability for ongoing treatment with a permanent surgically implanted nerve stimulator. Performance and documentation of an effective trial is a prerequisite for permanent nerve stimulation. In situations where the spinal cord stimulator has been working well but is in need of replacement	Selection of patients for implantation of spinal cord stimulators is critical to success of this therapy. SCS therapy should be considered as a late option after more conservative attempts such as medications, physical therapy, psychological therapy or other modalities have been tried. Patients must have undergone careful screening, evaluation and diagnosis by a multidisciplinary team prior to implantation. (Such

			for battery change, malfunction or end of stimulator life, a new trial is not needed to replace the stimulator.	screening must include psychological, as well as physical evaluation). Documentation of the history and careful screening must be available in the patient chart if requested. Patients being selected for a trial: Must not have active substance abuse issues. Must undergo proper patient education, discussion, and disclosure including an extensive discussion of the risks and benefits of this therapy. Must undergo appropriate psychological screening
Aetna Spinal Cord Stimulation (0194) Last review: 07/13/2023 Next review: 02/08/2024	NR	Yes	Aetna considers the following medically necessary: Trial implantation of a percutaneous dorsal column stimulator for patients with FBSS, CRPS, inoperable chronic ischemic limb pain secondary to peripheral vascular disease, Last resort treatment of moderate to severe (5 or more on a10-point VAS scale) chronic neuropathic pain of certain origins (i.e., lumbosacral arachnoiditis, phantom limb/stump pain, peripheral neuropathy (including diabetic peripheral neuropathy), post-herpetic neuralgia, intercostal neuralgia, cauda equina injury, incomplete	Dorsal column stimulators using high-frequency spinal cord stimulation (Senza), burst stimulation (BurstDR)) or differential target multiplexed stimulation (Medtronic DTM) are considered equally effective alternatives to standard dorsal column stimulators for the indications listed above. Replacement of a functioning standard dorsal column stimulator with a high-frequency, burst dorsal

			spinal cord injury, or plexopathy) that has been present for 12 or more months who have undergone careful screening, evaluation, and diagnosis by a multidisciplinary team, have no substance abuse disorders, have obtained clearance from a qualified mental health professional, have had unsuccessful conservative therapy for 6 months, have a documented pathology, have an ODI score of at least 21% Implantation of a permanent dorsal column stimulator in patients meeting the above criteria who experienced 50% or more pain reduction in the trial period Use of a dorsal column stimulator for management of intractable angina in patients with unresponsive pain who are not candidates for surgery who experienced 50% or greater pain reduction in the trial period, have angiographically documented significant coronary artery disease not suitable for revascularization procedures, have had optimal pharmacotherapy for at least one month (includes maximal tolerated doses of at least two of long-acting nitrates, beta-adrenergic blockers, or calcium channel antagonists), have New York Heart Association Functional Class III or IV angina pectoralis, and have reversible ischemia documented by symptom-limited treadmill exercise test	column or DTM stimulator is considered not medically necessary The following are considered experimental and investigational: cervical trauma, disc herniation, essential tremor, failed cervical spine surgery syndrome presenting with arm pain, neck pain, cervicogenic headache, gliomas, migraine, radiation-induced brain injury, stroke, trigeminal neuropathy, chronic pancreatitis, treatment of persons in a chronic vegetative or minimally conscious state, chest wall/sternal pain, chronic abdominal pain, chronic limb ischemia, chronic malignant pain, chronic pelvic pain, chronic visceral pain, coccydynia, gait disorders, gastroparesis, Guillain Barre syndrome, irritable bowel syndrome, meralgia paresthetica, neurodegenerative ataxia, multiple sclerosis, orthostatic tremor, Parkinson's disease, peri-rectal pain, sleep disorders, Sphincter of Odi dysfunction, ventricular fibrillation,

			Replacement and removal (including removal where not initially indicated) of dorsal column stimulators Spinal cord stimulator patient programmer for members meeting criteria	ventricular tachycardia, use of intra-operative motor-evoked potentials and somatosensory-evoked potentials, concurrent use of two dorsal column stimulators
Cigna Musculoskeletal Spinal Cord and Dorsal Root Ganglion Stimulation (CMM-211) Last review: 07/01/2021 Next review: NR	NR	Yes	A dorsal column stimulator capable of using either high-frequency or non-high-frequency stimulation (dual-mode) is considered an equally effective alternative for the treatment of any of the medically necessary indications listed, when the device uses non-high-frequency stimulation: FBSS (Trial: Failure of 6 consecutive months physician-supervised conservative treatment, surgery not indicated or desired, attestation of sufficient mental health (including substance abuse) by behavioral health provider; Permanent: At least 50% reduction in pain during trial period); CRPS (Trial: Must have diagnosis evidenced by continuing pain disproportionate to inciting event, at least one each sensory (hyperesthesia), vasomotor (temperature asymmetry, skin color changes/asymmetry), sudomotor/edema (edema, sweating changes/asymmetry), motor/trophic (decreased range of motion, motor dysfunction, trophic changes) symptoms reported and at least two symptoms shown on physical examination, failure of 6 consecutive months physician-supervised conservative treatment, surgery not indicated or desired, attestation of sufficient	High frequency SCS is considered experimental, investigational, or unproven for any non-FBSS indication. SCS is considered experimental, investigational, or unproven for post-amputation pain, post-herpetic neuralgia, peripheral neuropathy, dysesthesias involving lower extremities secondary to spinal cord injury, abdominal/pelvic visceral pain, chronic cervical or lumbar radiculopathy without prior spinal surgery, failed cervical and/or thoracic surgery with intractable neuropathic pain in arms or trunk Replacement of a functioning SCS with a high-frequency SCS is considered not medically necessary

			mental health (including substance abuse) by behavioral health provider; Permanent: At least 50% reduction in pain during trial period); Chronic critical limb ischemia (Trial: Attestation from vascular surgeon that individual is not suitable for vascular reconstruction, diagnosis of critical limb ischemia with ischemic limb rest pain, Rutherford Classification Grade II, Category 4 ischemic rest pain characterized by both resting ankle pressure <40mmHg, flat or barely pulsatile ankle or metatarsal pulse volume recording and toe pressure <30mmHg, angiographic or CT/MR imaging demonstrating multi-level disease with absence of named vessel with flow into the foot, attestation of sufficient mental health (including substance abuse) by behavioral health provider; Permanent: beneficial clinical response from a temporarily implanted electrode has been demonstrated); Chronic stable angina pectoris (Canadian Cardiovascular Society functional class III or IV, attestation from treating cardiologist confirming significant coronary artery disease and no suitability for revascularization procedure, failure of optimal pharmacological treatment using anti-anginal medications (long-acting nitrates, beta-adrenergic blockers, calcium-channel antagonists) to adequately improve symptoms, attestation of sufficient mental health (including substance abuse) by	

			behavioral health provider; Permanent: Beneficial clinical response from a temporarily implanted electrode has been demonstrated) A dorsal column stimulator using high frequency is considered an equally effective alternative to non-high-frequency stimulation only for the treatment of chronic intractable pain, secondary to failed back surgery syndrome (FBSS) as noted above Replacement of malfunctioning/irreparable stimulators and electrode arrays, plates, and paddles is considered medically necessary	

CMS = Centers for Medicare Services; CRPS = Complex region pain syndrome; CT – computed tomography; DTM = Differential target multiplexed stimulation; FBSS = Failed back surgery syndrome; MRI = magnetic resonance imaging; NR = Not reported; ODI = Oswestry Disability Index; SCS = Spinal cord stimulator; VAS = Visual analogue scale.

3 The Evidence

3.1 Methods of the Systematic Literature Review

3.1.1 Objectives

The aim of this report is to systematically review, critically appraise, analyze, and synthesize research evidence evaluating the effectiveness and safety of SCS for treatment of pain related to failed back surgery syndrome (FBSS), chronic back pain, complex regional pain syndrome (CRPS), or peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia) in adults who are SCS-naive. The differential effectiveness and safety of these therapies for subpopulations was evaluated, as was the cost effectiveness.

3.1.2 Key Questions

When used in adult patients who have failed other treatment options for pain related to FBSS, chronic back pain, CRPS, or peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia):

1. What is the evidence of short and long-term effectiveness of SCS compared with medical and/or surgical treatment (appropriate to condition) that does not include neuromodulation devices?
2. What is the evidence of the safety of SCS compared with medical and/or surgical treatment (appropriate to condition) that does not include neuromodulation devices?
3. What is the evidence that SCS has differential efficacy or safety issues in sub-populations of interest?
4. What is the evidence of cost-effectiveness of SCS compared with other medical or surgical options that do not include neuromodulation?

3.1.3 Inclusion/Exclusion Criteria

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. Public comments as well as those from clinical experts and peer-reviewers were considered for finalization of this report. See Table 7 below for inclusion and exclusion criteria.

Table 7. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Adults with one of the following: • chronic low back pain, failed back surgery syndrome* with low back pain and significant radicular pain, complex regional pain syndrome, peripheral neuropathy (phantom limb or stump pain, diabetic neuropathy or postherpetic neuralgia) Special populations/factors of interest: Sex, age, psychological or psychosocial co-morbidities, diagnosis or pain type, provider type, setting or other provider characteristics, health care system type, including worker's compensation, Medicaid, state, employees	• Children, patients <18 years old • Patients with prior use of SCS • Patients who are pregnant • All other pain conditions (e.g., cancer pain, chronic refractory anginal pain, heart failure, critical limb ischemia, peripheral vascular pain, pain at end of life, MS, fibromyalgia, headache, trigeminal neuralgia, chronic pancreatitis, chronic pelvic pain, chronic abdominal pain, post-stroke pain • Studies in which < 75% of patients have chronic musculoskeletal or neuropathic pain or other included pain conditions and results for patients with these conditions are not reported separately
Intervention	FDA-approved spinal cord stimulation (permanently implanted pulse generator systems and radiofrequency receiver systems)	• Temporarily implanted spinal cord stimulation devices • Neurostimulation of other parts of the nervous system (e.g., peripheral nerves, deep brain), dorsal root ganglion stimulation • Transcutaneous electrical nerve stimulation (TENS) • Non-FDA approved devices (unless final, phase III trial) • Intrathecal pumps
Comparator	Medical and/or surgical treatment (appropriate to condition) that does not include comparison of SCS methods/devices or other neuromodulation devices	• Comparisons of SCS devices • Comparison of SCS combined with other interventions vs. the other intervention alone • Comparisons of different types/modalities of SCS (e.g., comparisons of low versus high frequency, burst vs. tonic, etc.)
Outcomes	**Primary Outcomes (SOE)** • Function • Pain • Opioid use • Complications and adverse effects (e.g., procedural complications and technical failures, harms, infection, revision, removal, painful paresthesia or loss of paresthesia, mortality, serious adverse events) **Secondary outcomes (No SOE)** • Health-related quality of life (HR-QoL) • Anxiety and depression • Patient satisfaction	• Non-clinical outcomes • Non-validated measures • Intermediate outcomes • Return to work

Study Component	Inclusion	Exclusion
	• Global perceived effect (GPE)/global impression of change	
Setting	Any	
Study design	• RCTs will be the primary focus; prospective high quality comparative nonrandomized studies of intervention (NRSI) with concurrent controls that control for confounding will be considered if RCTs are not available; question 3 is limited to RCTs) • NRSIs including case series designed to evaluate harms with at least 5 years follow-up, or which report on rare harms for question 2 • Formal cost-effectiveness analyses assessing initial placement and replacement will be considered for question 4	• Case reports • Case series (for KQ1, 3, 4) • Case series not designed to evaluate harms, those with < 5 years follow-up for question 2 unless they report on rare harms outcomes • Non-clinical studies (e.g., animal studies) • Studies with N <10 patients total or <10 per group • Studies not reporting on primary outcomes or harms
Publication	• Studies published in English in peer reviewed journals, published HTAs or publicly available FDA reports • Full formal economic analyses (e.g., cost-utility analyses) published in English in an HTA, or in a peer-reviewed journal published after those represented in previous HTAs	• Abstracts, editorials, letters, books, conference proceedings • Studies without abstracts available online • 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/publications • Other types of economic evaluations (e.g., costing studies, cost-minimization analyses, cost-benefit analyses)

DRGS = Dorsal Root Ganglion Stimulation; FDA = Food and Drug Administration; GPE = Global perceived effect; HFSCS = High-frequency spinal cord stimulation; HR-QoL = Health-related quality of life; HTA = Health Technology Assessment; MS = multiple sclerosis; NRSI = Non-randomized studies of interventions; RCT = Randomized Control Trial; SCS = Spinal cord stimulator; SOE = Strength of Evidence; TENS = Transcutaneous electrical nerve stimulation.
*Definitions of FBSS across studies vary.

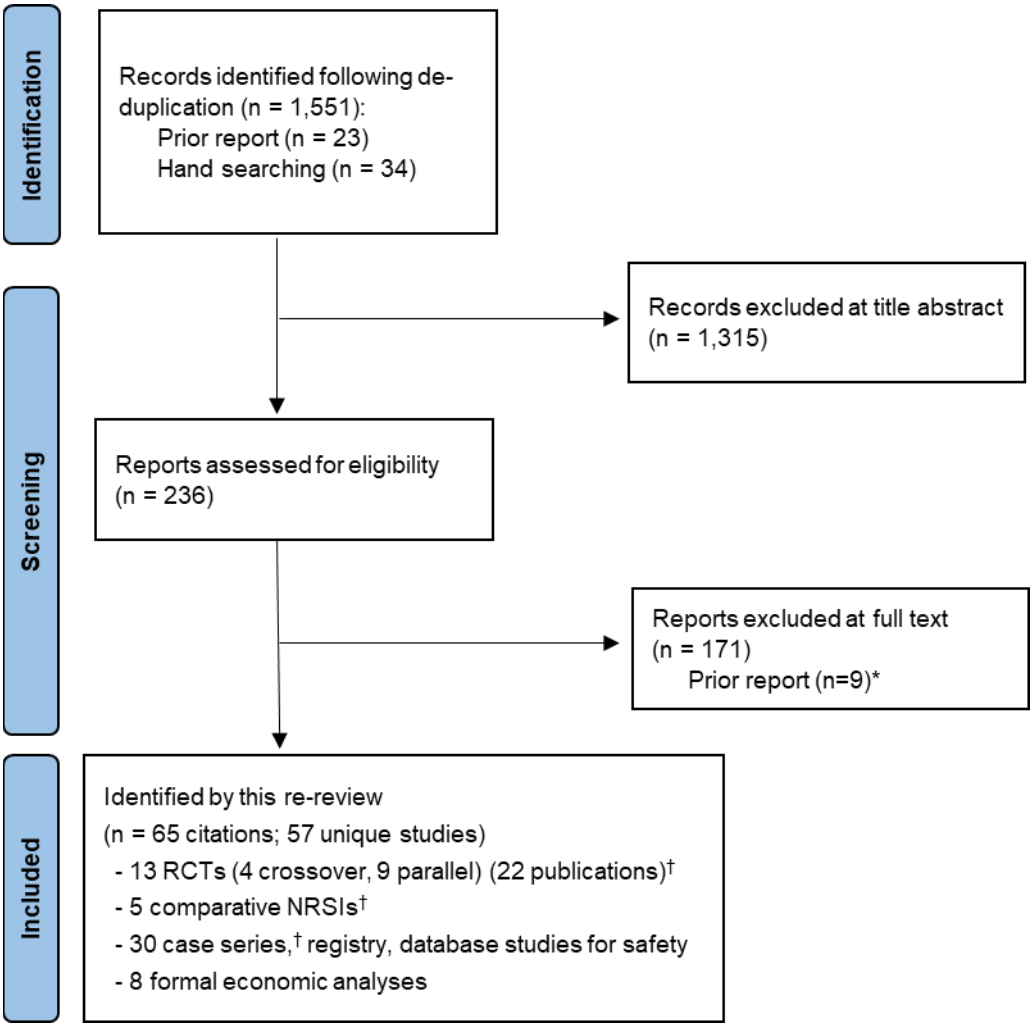
3.1.4 Data Sources and Search Strategy

We searched electronic databases from 2010 to June 6, 2023 to identify publications evaluating SCS treatments for chronic low back pain, failed back surgery syndrome with low back pain and significant radicular pain, complex regional pain syndrome, and peripheral neuropathy that had been published since the prior report. The start date of our search overlaps by a few months with the end date of the searches in the prior report. A formal, structured systematic search of the peer-reviewed literature was

performed across a number of databases including PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (see Appendix B for full search strategy) to identify relevant peer reviewed literature as well as other sources (ClinicalTrials.gov, ECRI Guidelines Trust, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The process involves four stages. The first stage of the study selection process consisted of the comprehensive electronic search and bibliography review. 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 were included for full-text review. We excluded conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations. 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 review and selection of those studies using a set of *a priori* inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary, adjudicated by a third investigator. See Figure 1 below for a flow diagram of the search results. A list of excluded articles along with the reason for exclusion is available in Appendix C. The remaining articles form the evidence base for this report.

Figure 1. Flow of studies diagram



NRSI = nonrandomized studies of interventions; RCT = Randomized controlled trial
*6 prognostic studies and 3 economic studies included in the prior report were excluded from this re-review. Prognostic studies were not part of the scope of this re-review. The economic trials from the prior report were not formally included but are summarized with the other economic studies.
†3 parallel RCT (in 7 publications), 1 prospective comparative NRSI and 6 case series were carried over from the prior report.

3.1.5 Data Extraction

Reviewers extracted the following data from the clinical studies: study design, setting, country, source of funding, sample size, inclusion and exclusion criteria, study population characteristics, follow-up time, SCS information, study outcomes and adverse events. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting data from the same study. Detailed study and patient characteristics and results are available in Appendix G.

3.1.6 Quality Assessment: Risk of Bias (RoB), Overall Strength of Evidence (SOE), and QHES evaluation

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria[175] based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[67]and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[3] For parallel group RCTs criteria include adequate methods for randomization, allocation concealment, blinding, baseline comparability between study arms and completeness of follow-up. Additional potential sources of bias unique to crossover trials were evaluated based on Cochrane methods. Such sources include evaluation of group comparability after the first phase/period, incorporation of a sufficiently long washout period, mitigation of carryover effects and/or testing for carryover effects, use of correlated data analyses. For comparative NRSIs, patient sampling/inclusion methods, baseline comparability between treatment groups and control for confounding were assessed. Case series were considered at high risk of bias and not individually assessed (Appendix E). In keeping with the AHRQ methods, each study was given a final rating of "good", "fair", or "poor" quality as described below. Discrepancies in ratings between reviewers were resolved through discussion by two or more investigators and to reach consensus. Criteria are detailed in Appendix D.

Table 8. Criteria for Grading the Quality of Individual Studies

Rating	Description and Criteria
Good	• Low risk of bias; study results generally considered valid • Employed valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics/key risk factors for testing groups being compared; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinded outcomes assessment); and use appropriate analytic methods (e.g., intention-to-test analysis); full reporting on pre-specified outcomes • For studies of testing, pre-specification of thresholds for a positive test
Fair	• Study is susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • This category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; the study contains "fatal flaws" in design, analysis or reporting; large amounts of missing information; discrepancies in reporting or serious problems with intervention or test delivery • Study results are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. in conjunction with consideration of epidemiologic principles that may impact findings.[122] Based on these quality criteria, each comparative study chosen for inclusion for a Key Question was given a risk of bias (RoB) (or QHES) rating; details of each rating are available in Appendix E.

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[10,58,59] as outlined by the AHRQ.[3] The SOE was based on the highest quality evidence available for the primary outcomes.

In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias.
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head-to-head).
- **Precision:** describes the level of certainty surrounding the effect estimates. It considers the variability around effect estimates and the extent to which a clinically useful conclusion may be possible.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[14,139] Publication bias could not reliably be assessed across studies using graphical or statistical tests for small sample effects, therefore this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We are unable to estimate an effect, have no confidence in the effect estimate for this outcome or the body of evidence has unacceptable efficiencies precluding judgment;

Instances where all studies of a specific outcome were considered poor were rated as insufficient. Instances where there was no evidence were marked as such.

Assessing the SOE for studies performing subgroup analysis for evaluation of differential effectiveness or safety requires additional considerations discussed below. Methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

3.1.7 Analysis

Evidence was summarized qualitatively and quantitatively. Risk ratio (RR) and 95% confidence intervals were used for dichotomous outcomes to evaluate the presence of an association between testing and the outcome. In the absence of adjusted effect size estimates, for dichotomous outcomes, crude risk ratios (RR) and 95% confidence intervals (CI) were calculated using either STATA 14.0132 or Rothman Episheet.[1,151] For instances with fewer than five observations per cell, exact methods were employed. When effect estimates that were adjusted for confounding were reported by study authors, they were preferred and reported. For continuous variables, mean differences (MD) and associated 95% CIs were calculated if the outcomes were reported using the same scale.

Meta-analyses were conducted as appropriate in order to summarize primary outcome data from multiple studies and to obtain more precise and accurate estimates using STATA 14.0.[151] Due to the high rate of crossover in the parallel trials after the 6 month follow-up, the primary focus was on data and timepoints prior to crossover. For crossover trials, comparison between treatment groups following the first treatment period is preferable; none of the included crossover trials reported data for the first period, however. To determine the appropriateness of meta-analysis, clinical and methodological diversity were assessed as was statistical heterogeneity. Statistical heterogeneity among the studies was assessed using Cochran's χ^2 test and the I^2 statistic.[66] To combine trials, we used a random effects model based on the profile likelihood method which provides a more conservative effect estimate; in the case of non-convergence with profile likelihood, the Der Simonian and Laird estimates were reported.[63] For continuous variables, differences in mean follow-up scores between treatments were analyzed to determine mean differences as an effect size. Methods for calculating the standard deviations and for imputing missing standard deviations followed the recommendations given in The Cochrane Handbook 7.7.[67] Where no events occurred in one arm of a study, a value of 0.50 was used for that arm in accordance with Cochrane methods. Studies in which no events occurred in either study arm did not contribute to effect estimates (0% weight) but were retained in some plots for visual effect and completeness. Sensitivity analyses were conducted excluding poor-quality studies, outlying data and clinically heterogeneous trials to the extent that data permitted. We classified the magnitude of effects for continuous measures of pain and function using the same system as in prior AHRQ reviews on pain (Appendix J).[24,144,145] Effects below the threshold for small were categorized as no effect/no difference. Outcomes are detailed in the evidence tables in the appendices and/or the body of the report. We did not conduct analyses to evaluate potential markers for publication bias given the small number of trials available for some analyses.[152]

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Further, only

RCTs that formally tested for interaction between subgroups were considered for Key Question 3. No trials meeting our inclusion criteria that evaluated heterogeneity of treatment effect were identified.

4 Results

4.1 Number of Studies Retained and Comparison with Prior Report

From 1,551 unique citations identified from electronic database searches, hand searching and bibliography review of included studies a total of 38 studies (in 43 publications) that met our inclusion criteria were identified: 10 randomized controlled trials (RCTs) (in 15 publications),[5,21,33,39,62,78,89,117,126-128,133,147,148,167] four comparative nonrandomized studies of interventions (NRSIs),[37,97,125,177] and 24 case series, database or registry studies designed to evaluate safety. Together with 10 studies included in the prior HTA (see below for more details) a total of 49 studies, 13 RCTs (in 22 publications),[5,21,33,39,62,78,83-85,89,92,93,99,117,119,126-128,133,147,148,167] five comparative NRSIs (2 prospective and 3 retrospective)[37,97,125,164,177] and 30 single-arm case series,[13,23,43,55,60,69,82,88,94,95,98,102,116,120,131,135,137,161,166,169,180] database[6,47,52,61,73,96] and registry[20,34,130] studies were included in this re-review that evaluated the efficacy/effectiveness and/or safety of spinal cord stimulation (SCS). Table 9 below provides an overview of studies by condition, intervention, and comparator treatment and provides the funding source for the RCTs (69% were funded by industry). See Appendix E, Table E9 for details related to trial funding and author conflicts of interest. Most studies evaluated SCS for the treatment of chronic low back pain (CLBP), primarily failed back surgery syndrome (FBSS). The most common comparator treatment was conventional medical management (CMM) the components of which varied across the included studies. CMM was not standardized or provided in a controlled way and the actual CMM modalities that the patients received throughout the treatment period were not well reported in most studies. In addition, eight formal cost-effectiveness analyses were included, two in U.S. settings[70,124] (both CLBP populations) and six in non-U.S. settings.[9,36,86,91,134,146] The economic trials from the prior report were not formally included but are summarized with the other economic studies. No trials meeting the inclusion criteria that evaluated differential efficacy and safety were identified.

Regarding the RCTs, four were crossover trials[5,62,89,148] and nine (in 18 publications) were parallel trials.[21,33,39,78,83-85,92,93,99,117,119,126-128,133,147,167] The crossover trials compared different frequencies and modes (e.g. burst) of SCS versus a placebo/sham stimulation. Because of the difference in comparators and study designs, the crossover trials are reported separately from the parallel trials.

Comparison with the 2010 Spinal Cord Stimulation HTA

The evidence base for the prior SCS review included a total of three RCTs (7 publications) (2 FBSS and 1 CRPS-I)[83-85,92,93,99,119] and one prospective NRSI (FBSS in patients with open Washington state workers' compensation claims)[164] which provided data on efficacy/effectiveness and safety (Key Questions 1 and 2); in addition, six case series[82,94,95,98,120,137] with follow-up of five years or more were included for safety only (Key Question 2). All 10 studies included in the prior report evaluating efficacy/effectiveness and safety (Key Questions 1 and 2) were incorporated into the current review and all data was checked for accuracy. For evaluation of Key Question 3, the prior reported included six prognostic studies; however, our methods have evolved in the last decade regarding subgroup analyses and the evaluation of heterogeneity of treatment effect and these study designs do not answer the question of differential

effectiveness and safety. Prognostic studies were not part of the scope of this review. Three cost-effectiveness analyses were included to address Key Question 4.[118,143,155]

In general, the prior report found that SCS was superior to conventional therapies (CMM, physical therapy or reoperation) in the shorter term with respect to patient reported outcomes of pain but that the benefit of SCS decreased over time and was not significantly different from controls at longer term, though there was limited evidence available at later timepoints. Evidence for function and quality of life was sparse and results were inconsistent across trials. Regarding SCS safety, revision surgery and side effects were not uncommon through 5 years follow-up and mortality was rare. There were no trials comparing SCS with sham (i.e., crossover trials). The strength of evidence was primarily low. The results of this re-review are consistent with these findings.

Table 9. Overview of included studies addressing efficacy and effectiveness and/or safety

Condition Intervention vs. Comparator	No. RCTs (Pubs.)	RCT Industry Funded	No. Comp NRSI	No. Case series for safety
CHRONIC BACK PAIN				
Failed back surgery syndrome				
Crossover trials[*]				
SCS[†] vs. Sham	3[5,62,148]	1[5]	n/a	n/a
Parallel trials[*]				
Conventional SCS vs. CMM	2 (5)[92,93,99,117,133]	2[92,133]	4[37,125,164,177]	n/a
Conventional SCS vs. Reoperation	1[119]	1[119]	1[97]	n/a
Nonsurgical refractory back pain				
Parallel trials[*]				
HF (10 kHz)-SCS vs. CMM	1[78]	1[78]	0	n/a
TOTAL:	7 (10)[5,62,78,92,93,99,117,119,133,148]	5[5,78,92,119,133]	5[37,97,125,164,177]	n/a
PAINFUL DIABETIC NEUROPATHY				
Parallel trials[*]				
HF (10 kHz)-SCS vs. CMM	1 (3)[126-128]	1[127]	0	n/a
Conventional SCS vs. CMM	2 (4)[33,39,147,167]	2[33,147]	0	n/a
TOTAL:	3 (7)[33,39,126-128,147,167]	3[33,127,147]	0	n/a
COMPLEX REGIONAL PAIN SYNDROME				
Crossover trials[*]				
SCS[‡] vs. Sham	1[89]	1[89]	n/a	n/a
Parallel trials[*]				
HF (10 kHz)-SCS vs. CMM	1[21]	0	0	n/a
Conventional SCS vs. CMM	1[21]	0	0	n/a

Condition Intervention vs. Comparator	No. RCTs (Pubs.)	RCT Industry Funded	No. Comp NRSI	No. Case series for safety
Conventional SCS vs. PT	1 (3)[83-85]	0	0	n/a
TOTAL:	3 (5)[21,83-85,89]	1[89]	0	n/a
TOTAL OVERALL – *Crossover RCTs*	4[5,62,89,148]	50% (2/4)[5,89]		
– *Parallel RCTs*	9 (18)[21,33,39,78,83-85,92,93,99,117,119,126-128,133,147,167]	78% (7/9)[33,78,92,119,127,133,147]		
– *NRSIs*			5[37,97,125,164,177]	30[6,13,20,23,34,43,47,52,55,60,61,69,73,82,88,94-96,98,102,116,120,130,131,135,137,161,166,169,180]

CMM = conventional medical management; Comp = comparative; HF = high-frequency; PT = physical therapy; RCT: randomized control trial; SCS = spinal cord stimulation.
*Refers to RCTs only.
† Al-Kaisy 2018: Patients randomized to sham, 1200 Hz @ 18 µsec, 3030 Hz @ 60 µsec, or 5882 Hz @ 30 µsec. Hara 2020: Patients randomized to sham, burst (40 Hz, 4 spikes per burst). Sokal 2020: Patients randomized to sham, LF (40 to 60 Hz), HF (1000 Hz), or cluster tonic. Patients in Sokal 2020 were 78% FBSS and 22% CRPS, but classified under FBSS.
‡ Kriek 2016: Patients randomized to sham, 40 Hz, 500 Hz, 1200 Hz, or Burst.

4.2 Key Question 1: Efficacy and Effectiveness of SCS

4.2.1 Chronic Back Pain

Three crossover RCTs (N=98 randomized) were identified that met inclusion criteria that compared SCS with sham/placebo stimulation for treatment of FBBS[5,148] and chronic radiculopathy after surgery for degenerative lumbar spine disorders.[62]

A total of four parallel RCTs (in 7 publications) were identified that evaluated SCS for the treatment of chronic low back pain (CLBP).[78,92,93,99,117,119,133] Three RCTs included patients with lower back pain due to failed back surgery (i.e., failed back surgery syndrome [FBSS]) and compared conventional SCS versus CMM alone (2 RCTs)[92,133] and versus reoperation (1 RCT).[119] The fourth trial included patients without previous lumbar spine surgery who had failed all CMM treatments (the authors refer to this condition as "nonsurgical refractory back pain" [NSRBP]) and compared high-frequency (HF) (10 kHz) SCS in addition to CMM versus CMM alone.[78]

In addition, four comparative NRSIs were identified that evaluated the effectiveness of SCS compared with CMM for treatment of FBSS, two prospective NRSIs[125,164] and two retrospective, propensity score-matched database studies.[37,177]

4.2.1.1 SCS versus sham (placebo): Crossover RCTs

Three crossover RCTs (N=98 randomized) compared SCS with sham/placebo condition[5,62,148]. One RCT[5] specified FBSS as the indication for SCS and FBSS was the indication for 78% (18/23) of patients in second trial[148]; neither trial described diagnostic criteria. The population in the third trial was described as having chronic radiculopathy after surgery for degenerative lumbar spine disorders[62]. Mean age across

trials was 51 years old; the proportion of females ranged from 33% to 54%. Across trials, inclusion criteria included pain duration of ≥6 months. One industry-funded trial was conducted in the United Kingdom[5], one non-industry funded trial was conducted in Norway[62] and no funding was received for the third trial conducted in Poland[148].

The largest trial reported baseline daily pain medication use in 64% (32/50) of patients; opioid analgesics were used by 36% of patients, 34% of patients reported using gabapentinoids and 34% reported using acetaminophen (paracetamol) with only 10% reporting NSAID use[62]. Another trial reported that the total number of mediations did not differ between treatments (different SCS frequencies, sham)[148]. Authors report that approximately 49% of patients took opioids and 72% took NSAIDs based on models testing differences in medication intake during treatment periods. Changes in opioid or other medication use following treatment were not reported in either trial. Medication use was not reported in the other trial (N=24)[5].

All three RCTs excluded patients with active psychiatric or psychologic comorbidities and indicated that multidisciplinary teams were involved in determining suitability for SCS, however details of the assessment instruments, components and processes for patient screening were not consistently provided. The inclusion/exclusion criteria provide information patient selection that provides some insight regarding the screening process. (Appendix Table G11). All RCTs conducted a 14-to-17-day initial trial of SCS stimulation prior to permanent device implantation. Two trials required ≥50% reduction in pain[5,148] and the third[62] required ≥2 point improvement on NRS (0-10 scale) for leg pain for permanent implantation.

One trial[62] (N=50 randomized) compared burst SCS (40-Hz burst mode with 4 spikes/burst and an amplitude corresponding to 50% to 70% of the paresthesia perception threshold) with a placebo/sham exposure where no stimulation was applied. Patients received tonic stimulation during the testing period prior to permanent implantation. Of the 65 who underwent the SCS trial, 77% (n=50) received a non-rechargeable pulse generator as a permanent implant to deliver the burst stimulation and were randomized. There were two 12-week periods for each intervention (4 treatment periods).

One trial[5] randomized 24 patients with FBSS to four settings (sham, 1200 Hz @ 180 µsec, 3030 Hz @ 60 µsec or 5882 Hz @ 30 µsec) over four 3-week crossover phases over 12 weeks. Settings were generated using a custom-made programmer (Model 09070, Medtronic, Inc.) used exclusively for clinical investigations and allowed for a total of 24 unique treatment sequences. A total of 53 patients were recruited for trial stimulation with 68% (n=36) completing. Thirty-three patients were implanted with permanent implantable pulse generators (IPGs) upon passing the required threshold of ≥50% reduction in pain to succeed, and 57% (n=30) were randomized. Six patients were excluded due to early discontinuation, deviations from randomization, and programming challenges, with 24 (45%) patients in the final analyses.

The third trial[148] (N=18 randomized) included patients with either FBSS (78%) or complex regional pain syndrome (CRPS) (22%) and compared placebo with HF (1000 Hz), low frequency (LF) tonic (40 to 60 Hz) and what was termed 'clustered tonic' stimulation, described as a burst stimulation with 450 to 550 Hz in a cluster activated with 40 to 50 Hz. Twenty-three patients were initially enrolled, though only 17 underwent a trial stimulation, 94% (n=16/17) completed the trial stimulation, and 76% (n=13/17) were successful upon a ≥50% reduction in pain. The other six patients were unable to undergo percutaneous implantation and underwent a one-stage surgery implanting a surgical paddle electrode and permanent IPG in the subcutaneous pocket, though one of them dropped out of the study. The final randomization

and analyses included the 13 patients with successful trial stimulation and five patients that were unable to undergo trial stimulation.

One trial was rated good,[62] two trials were rated fair[5,89] and one was rated as poor[148] quality. Study limitations include lack of distinct washout period between treatments and lack of data from the first phase/set of sequences; results are reported across all treatment sequences. Statistical analyses accounting for correlated data were done in all trials. Two trials did not appear to report protocol-specified outcomes. Only one trial evaluated the potential for period effects.[5] The true potential for period and carryover in all trials is likely unknown. Information on randomization, allocation concealment and assessor blinding were unclear in the poor-quality trial.[148]

4.2.1.1.1 Pain

4.2.1.1.1.1 Back pain (0-10 scale)

Back pain was similar between the burst SCS and sham sequences, mean difference (MD) −0.2 (95% CI −0.7 to 0.2) in one trial[62]. Direct comparisons adjusting for repeated measures/correlated data between different SCS frequencies (1200 Hz, 3030 HZ, 5882 Hz) and sham that included confidence intervals were not reported in another trial[5]. Authors conclude that the high frequency (5882 Hz) phase conferred statistically greater pain relief compared with the active frequencies and sham (p=0.002) and that pain relief was similar for other frequencies and sham. Authors state that a mean pain score difference of 2 (0-10 scale) was considered clinically significant. The mean differences between individual frequencies and sham were not reported with corresponding confidence intervals. Effect estimates and confidence intervals based on the authors' raw arithmetic means and standard deviations reveal no differences between either the 1200 Hz or 3030 versus sham/placebo, however a moderate improvement in back pain is noted with the highest frequency (5882 Hz) compared with sham (MD -1.61, 95% CI -2.67 to -0.55). The authors' MD for this comparison appears to be adjusted for correlated data however no CI was provided; the CI here was back calculated using the reported p-value. A recent systematic review[162] that imputed data and statistically adjusted for correlated found no statistically significant difference between individual frequencies and sham conditions, including the comparison between the HF-SCS and sham (MD -1.6, 95% CI -3.48 to 0.26). Confidence intervals for both the estimate based on reported means and calculated estimates from the Cochrane review encompass a range of effects that includes those below a clinically meaningful threshold and a large effect, based on the magnitude of effect size described in the methods, suggesting substantial imprecision (Table 10). In the same trial[5], reported mean percent pain reduction across the frequencies was 40.6%, 39.8% and 57.1% for the 1200 Hz, 3030 Hz and 5882 Hz frequencies respectively, and 34.9% for sham. The authors report that 16.7% (4/24) of patients felt stimulation sensations during the sham phase. A test for interaction between treatment and period was not statistically significant.

4.2.1.1.1.2 Leg Pain (0-10 scale)

VAS leg pain improvement was similar between burst SCS and sham in one trial[62] (MD −0.2, 95% CI −0.7 to 0.2). Mean leg pain scores were also similar across SCS frequencies (1200 Hz, 3030 Hz, 5882 Hz) and sham in another trial (2.37, 2.20, 1.81, 2.51 respectively, p=0.367) in another trial[5] (Table 10).

4.2.1.1.1.3 Pain (not specified, 0-10 scale)

One poor-quality trial (N=18)[148] which compared three different forms of SCS delivery – HF (1000 Hz), LF tonic stimulation (40-60 Hz conventional) and clustered tonic stimulation – to a sham phase reported that pain reduction relative to baseline was comparable across the treatments and sham based on observed values and in various models that used Bayesian methods. Adjusted estimates from the recent systematic review reveal similar results between SCS modes and sham; imprecision is again noted (Table 10). The mean percent pain reduction by treatment phase was 1000 Hz, 37%; LF tonic, 50%; cluster Tonic, 34%; and sham, 34%. The author's models indicated that average pain did not substantially differ by treatment and was stable throughout the trial.

4.2.1.1.2 Function

The largest RCT found a similar improvement in function between the burst stimulation and sham sequences based on the Oswestry Disability Index (ODI, scale 0-100, MD in change scores -1.3, 95% CI -3.9 to 1.3)[62]. The other trials did not provide comparative information on measures of function (Table 10).

4.2.1.1.3 Opioid use

Changes in opioid or other mediation use following treatment phases were not reported in any trial.

4.2.1.1.4 Secondary outcomes

Quality of life: One trial[62] reported similar scores between burst SCS and sham on the EQ-5D index (0 to 1 scale); MD 0.04 (95% CI -0.08 to 0.16).

Patient Global Impression of Change and Patient satisfaction: One trial evaluated Patients Global Impression of Change and report a statistically significant difference across treatments in the ratings (p=0.007)[5]. No change was reported most frequently during sham exposure while more patients reported being better with the 5882 Hz. The proportion of patients who indicated that they were very satisfied or somewhat satisfied with each treatment was similar across groups with 63%, 75%, 75% and 63% respectively for the 1200 Hz, 3030 Hz, 5882Hz and sham conditions (p=0.672) (Table 10).

Table 10. Summary of outcomes comparing SCS vs. sham for crossover trials: FBSS, chronic radiculopathy after spine surgery

Outcome	Author, year (N) Quality	Period length	SCS type	SCS Mean (95% CI, SD or range)	Sham Mean (95% CI, CI, SD or range)	MD (95% CI, unadjusted unless noted)	MD (95% CI Calculated) Traeger – Cochrane
Primary outcomes							
Function (ODI, 0-100)	Hara, 2022 (N=50) Good	2, 12-week periods	Burst, 40 HZ, 4 spikes per burst	34.0 (95% CI 30.0 to 38.1) Δ from baseline -10 (95% CI -14 to 7.2)	35.4 (95% CI 31.3 to 39.4) Δ from baseline -9.3 (95% CI -12.7 to -5.9)	Adjusted Between group (MD in change scores) -1.3 (95% CI -3.9 to 1.3), p=0.32*	Between group (MD in change scores) -1.3 (-3.9 to 1.3), p=0.32
Back Pain VAS (0-10 scale)	Hara, 2022 (N=50) Good	2, 12-week periods	Burst, 40 HZ, 4 spikes per burst	5.9 (95% CI 5.3 to 6.4)	6.1 (95% CI 5.6 to 6.6)	Adjusted MD −0.4 (95% CI −0.8 to 0.04), p=0.07	-0.4 (-0.82 to 0.02)
	Al-Kaisy 2018† (N= 24) Fair	4, 3-week periods	1200 Hz	mean (SD), range 4.51 (1.87), range 0.07 to 7.03	mean (SD), range 4.83 (2.45), range 0 to 9.43	MD -0.32 (95% CI -1.59 to 0.94) (CI calculated from reported raw scores)	-0.32 (-2.17 to 1.54)
			3030 Hz	4.57 (2.09), range 0.10 to 8.77		MD -0.26 (95% CI -1.58 to 1.06) (CI calculated from reported raw scores)	-0.26 (-2.1 to 1.63)
			5882 Hz	3.22 (1.98), range 0 to 6.30		Adjusted MD -1.61 (95% CI -2.67 to -0.55) (CI calculated based on author's reported p-value of 0.003)	-1.61 (-3.48 to 0.26)

Leg Pain VAS (0-10 scale)	Hara, 2022 (N=50) Good	2, 12-week periods	Burst, 40 HZ, 4 spikes per burst	Mean (95% CI) 5.9 (5.3 to 6.4)	Mean (95% CI) 6.1 (5.6 to 6.6)	Adjusted: MD, −0.2 (95% CI −0.7 to 0.2), p=0.32	-0.20 (-0.65 to 0.25)
	Al-Kaisy 2018 (N= 24)‡ Fair	4, 3-week periods	1200 Hz	Mean (SD or CI) 2.37 (NR)	Mean (SD or CI) 2.51 (NR)	Not calculated (SD not provided)	-0.14 (-2.18 to 1.9)
			3030 Hz	2.20 (NR)			-0.31 (-2.35 to 1.73)
			5882 Hz	1.81 (NR)			-0.7 (-2.74 to 1.34)
Pain (NOS) VAS (0-10 scale)	Sokal 2020§ (N=18) Poor	4, 2-week periods	1000 Hz	Mean (SD) 5.17 (1.42) Δ from baseline 3.04 (1.47);	Mean (SD) 5.42 (1.22) Δ from baseline 2.73 (1.70)	MD -0.25 (95% CI -1.15 to 0.65)	-0.17 (-0.77 to 0.43)
			LF Tonic	4.18 (1.76) Δ from baseline 4.07 (2.11);		MD -1.24 (95% CI -2.27 to -0.21)	-0.99 (-2.25 to 0.27)
			Cluster Tonic (Burst)	5.27 (1.33) Δ from baseline 2.80 (1.63);		MD -0.15 (95% CI, -1.01 to 0.71)	-0.03 (-1.06 to 1.0)
				Percent	**Percent**		
Percent VAS back pain reduction (0-10)	Al-Kaisy 2018 (N= 24) Fair	4, 3-week periods	1200 Hz	40.6%	34.9%	Not calculated	Not calculated
			3030 Hz	39.8%		Not calculated	Not calculated
			5882 Hz	57.1%		Not calculated	Not calculated
Percent VAS pain reduction (NOS,0-10)	Sokal 2020 (N=18) Poor	4, 2-week periods	1000Hz	37%	34%	Not calculated	Not calculated
			LF Tonic	50%		Not calculated	Not calculated
			Cluster Tonic (Burst)	34%		Not calculated	Not calculated
Secondary Outcomes							
EQ-5D	Hara, 2022 (N=50) Good	2, 12-week periods	Burst, 40 HZ, 4 spikes per burst	Mean, 95%CI 0.48 (0.39 to 0.56)	Mean, 95%CI 0.44 (0.35 to 0.53)	(adjusted) MD, 95% CI 0.04 (95% CI -0.08 to 0.16), p=0.32	0.04 (-0.08 to 0.16)

Patients Global Impression of Change	Al-Kaisy 2018 (N= 24) Fair	4, 3- week periods	1200 Hz 3030 Hz 5882 Hz	% (n/N) No change 1200 Hz: 25% (6/24) 3030 Hz: 16.7% (4/24) 5882 Hz: 8.3% (2/24) Somewhat Better 1200 Hz: 58.3% (14/24) 3030 Hz: 70.8% (17/24) 5882 Hz: 50% (12/24) Better 1200 Hz: 16.7% (4/24) 3030 Hz: 12.5% (3/24) 5882 Hz: 41.7% (10/24)	% (n/N) No change 37.5% (9/24) Somewhat Better 41.7% (10/24) Better 20.8% (5/24)	Authors report PGIC scores were statistically different across treatment groups (p=0.007) with more rating their change as "better" following the 5882 Hz while more reported "no change" following the sham condition.	Not calculated
Patient satisfaction; very or somewhat satisfied	Al-Kaisy 2018 (N= 24) Fair			1200 Hz: 63% 3030 Hz: 75% 5882 Hz: 75%	63%	Similar rates of satisfaction across groups (p= 0.672)	Not calculated

CI = confidence interval; EQ-5D = EuroQol 5D; Hz=Hertz, MD = mean difference; NOS = Not otherwise specified; ODI= Oswestry Disability Index; PGIC = Patient's Global Impression of Change; RR = Risk ratio, SCS = Spinal cord stimulator; SD = Standard deviation; VAS = Visual analogue scale.

*it is unclear if this author reported difference was adjusted.

† P-value (model across frequency groups) p=0.002; Authors conclude that 5882 Hz produced significant pain relief vs. other frequencies and sham and that sham and the other frequencies produced similar analgesic effects.

‡ Authors report no different between mean leg pain scores during crossover phase among frequency groups, p = 0.367.

§ Authors report that reduction of pain was comparable between treatments, including placebo (statistical testing NR).

4.2.1.2 SCS versus CMM: Parallel RCTs and comparative NRSIs

Three parallel RCTs, two in patients with FBSS receiving conventional SCS[92,133] and one in patients with NSRBP receiving HF 10 kHz SCS,[78] and four comparative NRSIs[37,125,164,177] evaluated the efficacy and effectiveness of SCS versus CMM. For the RCTs, details regarding study inclusion and exclusion criteria can be found in Appendix Tables G12 and G13 and study characteristics/patient demographics summary tables can be found in Appendix Tables G2 to G5 (Summary tables: Appendix Tables G7 to G10).

Two RCTs (in 4 publications)[92,93,99,133] compared conventional SCS (in addition to CMM) with CMM alone for the treatment of moderate to severe low back pain due to FBSS. Sample sizes ranged from 100 to 218 (Total N=318). The average patient age was 53 years (range, 50 to 54 years) and 57 percent were female (range, 49% to 61%). One trial (PROMISE trial) enrolled patients with back pain greater than their leg pain.[133] The primary indication for initial surgery in this trial was disc herniation (50%) and it had been 5 years since the last back surgery (with an average symptom duration of 7 years); patients had undergone an average of two back surgeries prior to enrollment. Previous surgeries included fusion or disk replacement (68.5%) and nonfusion (31.2%; discectomy, laminectomy, laminotomy, foraminotomy, foraminotomy, and other). The second trial (PROCESS trial) enrolled patients with radiculopathy and leg pain greater than their back pain. Patients in this trial were required to be symptomatic for at least 6 months (mean duration not reported) and it had been a mean of 5 years since the last back surgery; 50 percent of patients had undergone more than one back surgery.[92] The article did not provide details regarding the precipitating condition or type of surgical interventions received. In one trial, 38 percent of participants were using opioids at study baseline[92]; the second trial did not report on medication use.[133] Comorbidities and prior failure of conventional medical management were not reported by either trial although patients with a history of coagulation disorder or evidence of an active psychiatric disorder were excluded.

The SCS trial period was a minimum of 3 days in one trial[133] and the duration was not reported in the other trial[92]; 82 percent of participants (range, 82% to 83%) experienced a successful trial leading to permanent SCS device implantation in 80 percent. Eight participants in one trial[133] experienced successful SCS trials but did not receive a permanent device (reasons unknown) and one trial[92] provided permanent implants to five participants who failed the trial but requested permanent implants. Appendix Table G7 provides details regarding SCS trial success criteria and SCS and CMM treatment parameters. Across all trials, CMM was not standardized, was provided at the treating physicians discretion, and could include a wide variety of treatment modalities. The follow-up period was 24 months and both trials allowed crossover of groups at 6 months; five percent (range, 2.4% to 10%) of participants randomized to SCS and 73 percent of participants (in both trials) randomized to CMM chose to do so.

One trial (PROMISE trial) was conducted at 28 sites across the U.S., Europe, Canada, and Columbia[133] and the other (PROCESS trial) was conducted at 12 sites across Europe, Canada, Australia and Israel[92]. Both RCTs were industry funded and indicated considerable involvement of the funding source in the research process; additionally, many authors had industry-based conflicts of interest. Both trials were rated fair quality with the biggest limitation being the inability to blind providers and patients (who were also outcome assessors given the self-report nature of the outcomes). In addition, there was differential loss

to follow-up between groups in one trial (greater attrition in the SCS group)[133] and baseline imbalances between treatment groups in the other trial.[92] See Appendix Table E2 for details on study quality.

The third RCT (N=159) compared HF (10 kHz) SCS in additional to CMM versus CMM alone in patients with chronic, axial, low-back pain with a neuropathic component and no previous spine surgery, deemed "nonsurgical refractory back pain" (NSRBP) by the authors.[78] The median patient age was 56 years, 57 percent were female and 93 percent were White. At study entry, 52 percent of participants were using opioids. Patient diagnoses included a combination of degenerative disc disease (70%), spondylosis (65%), radiculopathy (43%), and mild/moderate spinal stenosis (30%) primarily. Pain duration was mean of 8.3 years. All participants had failed CMM prior to inclusion and 86 percent were not surgical candidates due to underlying comorbidities or pathology/presentation. The SCS trial period was a maximum of 14 days and 93 percent of participants experienced a successful trial with 86 percent undergoing permanent SCS device implantation of the Senza 10Khz HF-SCS system. It is unclear whether the trial period used the same SCS device. Appendix Table G7 provides details regarding SCS trial success criteria and SCS and CMM treatment parameters. CMM was not standardized and could include a wide variety of treatment modalities. The follow-up period was 12 months and patients in both groups were allowed to crossover and receive the alternative treatment at 6 months; 89 percent of patents randomized to CMM crossed over to SCS (no SCS patient crossed over to CMM). This trial was conducted across 15 U.S centers, was industry-funded and multiple authors had industry-based conflicts of interest. This trial was rated fair quality with the biggest limitation being the inability to blind providers and patients (who were also outcome assessors given the self-report nature of the outcomes). In addition, there was differential loss to follow-up between groups (greater attrition in the SCS group). See Appendix Table E2 for details on study quality.

Additionally, two fair-quality prospective comparative NRSIs met inclusion criteria. For details on study and patient characteristic see Appendix Table G5 and for study quality ratings See Appendix Table E5. One NRSI (N=159)[164] compared conventional SCS compared to CMM or pain clinic-based management for the treatment of FBSS in WA State Workers' Compensation patients and was included in the prior report. Median participant age was 44 years and 23 percent were female. Participants had symptom duration of at least 6 months with an average of two prior back surgeries and 80 percent of participants were using opioids at baseline. Comorbidities and time since last operation were not reported. The SCS trial implantation period was not reported, and 52 percent of participants experienced a successful trial leading to permanent SCS device implantation with a device determined by the involved medical professional(s). It is unclear whether the trial period used the same SCS device. CMM received by patients was determined at the discretion of the medical professional(s) involved. Crossover was allowed immediately upon enrollment; 10 percent (5/52) of individuals assigned to SCS crossed over to the CMM treatments and four percent (4/107) of individuals assigned to the CMM arms crossed over to SCS. The second NRSI[125] (N=85) compared SCS to CMM. The mean age of participants was 57 years and 68% were female. Fewer SCS patients were female (54% vs. 80%). Mean symptom duration was 8.7 years. The SCS trial implantation period was 1 to 2 weeks, and patients were successful upon reporting 50% or greater pain reduction. Authors did not report the number of eligible patients that passed trial stimulation. In patients permanently implanted with IPGs, 83% received systems programmed to 40-70 Hz (280 to 420 microseconds, 3.8-6 mA), and the remaining 17% were programmed to 1000 Hz (200 microseconds, 2 mA). CMM included oral and intravenous pharmacological treatment (NSAIDs, opioids, muscle relaxants, anticonvulsants, and dual or tricyclic antidepressants), physical therapy, nerve block and trigger point block, epiduroscopy, radiofrequency, epidural procedures, and oxygen-ozone therapy. Patients maintained initial group allocation in accordance with ITT principles, though 1 (2%) in the CMM

arm received a neurostimulator implant and 3 (8%) in the SCS arm underwent further minor reoperations.

Details regarding study characteristics and patient populations for the two retrospective database studies[37,177] can be found in Appendix Table E6.

Given some of the inherent differences between conventional and HF (10 kHz) SCS, results are reported separately by type of intervention. Also, given the high frequency of crossover, the results that follow focus on the 6-month timepoint, prior to crossover; information regarding longer term outcomes in SCS patients can be found in Appendix Tables F2 and F6. These data are not comparative and are essentially case series of SCS. In general, the trials indicated that the improvements seen with SCS during the first 6 months were sustained longer term i.e., 12 months in the trial of HF (10 kHz) SCS for NSRBP[78] and 24 months in the two trials of conventional SCS for FBSS.[93,133] One of the latter trials also presented data for the CMM patients who crossed over to receive SCS and reported significant improvement in LBP through 24 months in this group.[133]

4.2.1.2.1 Pain

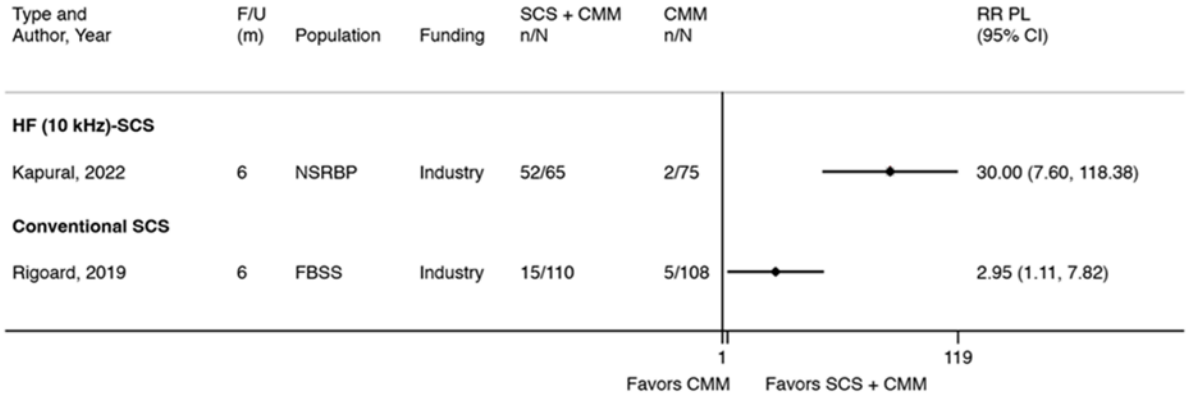
4.2.1.2.1.1 Pain Responders

Low back pain (LBP) responders

Two fair-quality trials, one evaluating HF (10 kHz)-SCS in patients with NSRBP[78] and one evaluating conventional SCS in patients with FBSS,[133] reported LBP pain "success" (responders) i.e., the proportion of patients in each group with ≥50% reduction in LBP on the VAS/NPRS (0-10). Both types of SCS were associated with a substantial increase in the likelihood of achieving pain response compared with CMM alone at all timepoints; the magnitude of effect was greater for HF (10 kHz)-SCS (compared with conventional SCS) however the effect estimates were extremely imprecise. LBP response was achieved by 74.3% of HF (10 kHz)-SCS patients versus 1.3% of CMM patients at 3 months in the ITT analysis (N=159, RR 56.77, 95% CI 8.07 to 399.46; completers analysis: N=143, 80.9% vs. 1.3%, RR 60.66, 95% CI 8.63 to 426.51) and 80% versus 2.7% at 6 months in the per-protocol (PP) analysis (i.e., completers analysis) (N=140, RR 30.00, 95% CI 7.60 to 118.38) (ITT not reported at this timepoint),[78] Figure 2. In the trial comparing conventional SCS versus CMM, 13.6% versus 4.6% of patients achieved LBP response at 6 months in the ITT analysis, Figure 2 (N=218, RR 2.95, 95% CI 1.11 to 7.82; completers analysis: N=196, 16.3% vs. 4.8%, RR 3.39, 95% CI 1.28 to 8.97).[133]

The trial evaluating conventional SCS in patients with FBSS also reported an "as treated" analysis which similarly favored SCS versus CMM alone (Appendix Table F2).[133]

Figure 2. Low back pain responders (≥50% reduction in LBP on the VAS/NPRS): SCS versus CMM for chronic back pain



CI = confidence interval; CMM = conventional medical management; FBSS = failed back surgery syndrome; F/U = follow-up; kHz = Kilohertz; m = months; NPRS = numerical pain rating scale; NSRBP = nonsurgical refractory back pain; PL = profile likelihood; RR = risk ratio; SCS = spinal cord stimulation; VAS = visual analog scale.

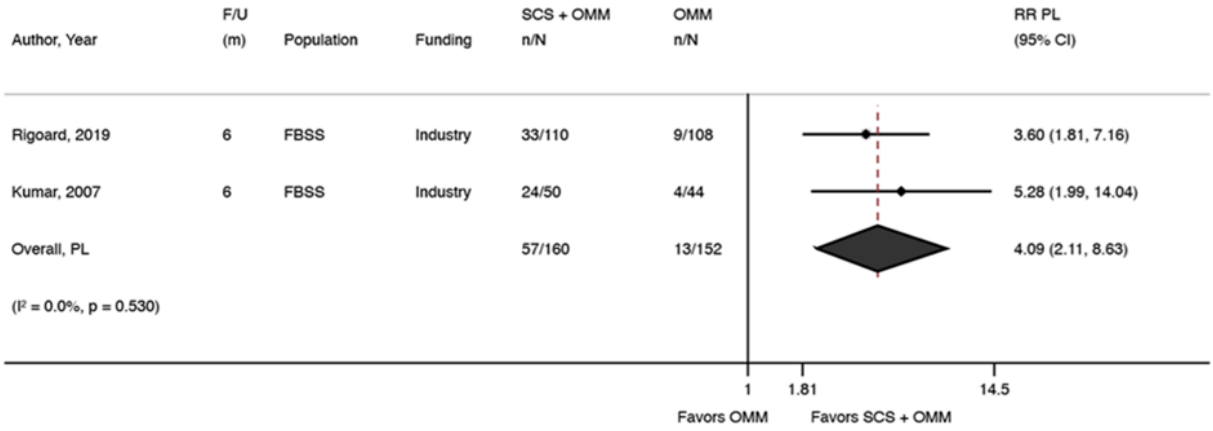
One trial reported alternative definitions of LBP pain success/response (i.e., ≥30% and ≥2-point improvement on NPRS) at 6 months which also showed a large effect favoring conventional SCS versus CMM alone for the treatment of FBSS (Appendix Table F10).[133]

In addition, one prospective comparative NRSI in patients with FBSS with radiculopathy, reported that substantially more patients who received SCS versus CMM achieved a reduction of at least 50% in pain at the present moment (according to VAS pain scale scores included in the PainDETECT questionnaire [PD-Q]) by 24 months (N=52, 36% vs. 4%, RR 7.9, 95% CI 1.09 to 57.52)[125]; the results were similar for the other two PD-Q VAS pain scales (strongest and average pain in the past month) (Appendix Table F5) Since the authors did not specify, we assume that these scores are evaluating back pain, as opposed to leg pain (most patients had radiculopathy). The authors also reported the proportion of patients who achieved a 30% or greater improvement (reduction) in PD-Q total scores by 24 months which similarly favored SCS (N=52, 48.7% vs. 8.7%, RR 5.6, 95% CI 1.40 to 22.00); the PD-Q measures the quality of neuropathic pain symptoms.

Leg pain responders

Two fair-quality trials that compared conventional SCS versus CMM in patients with FBSS reported leg pain "success" (responders) i.e., the proportion of patients in each group with ≥50% reduction in leg pain on the VAS/NPRS (0-10) based on ITT analyses.[92,133] SCS (plus CMM) was associated with a large increase in the likelihood of achieving leg pain response at 6 months versus CMM alone (N=312, 35.6% vs. 8.6%, RR 4.09, 95% CI 2.11 to 8.63, I^2=0%), Figure 3. One of these trials reported a similarly large increase favoring SCS at 3 months (56.0% vs. 9.1%, RR 6.16, 95% CI 2.34 to 16.19).[92]

Figure 3. Leg pain responders (≥50% reduction in LBP on the VAS/NPRS): SCS versus CMM for chronic back pain



CI = confidence interval; CMM = conventional medical management; FBSS = failed back surgery syndrome; F/U = follow-up; m = months; NPRS = numerical pain rating scale; PL = profile likelihood; RR = risk ratio; SCS = spinal cord stimulation; VAS = visual analog scale.

Both trials conducted various other analyses of the data at 6 months, all of which showed that SCS was associated with a significantly greater likelihood of achieving response compared with CMM alone (Appendix Table F2): per protocol (i.e., completers) and "as treated" analyses in one RCT[133] and a sensitivity analysis which excluded those patients in the SCS group who failed trial stimulation but requested permanent SCS implants (n=5) and a "worst-case" analysis (patients withdrawn in the SCS group were considered failures and in the CMM were considered successes) in the second RCT.[92]

One trial reported alternative cut-offs for leg pain success/response (i.e., ≥30% and ≥80% improvement on VAS) at 6 months which also showed a large effect favoring conventional SCS versus CMM alone for the treatment of FBSS (Appendix Table F2).[92]

In addition, one prospective, comparative NRSI that evaluated FBSS patients who had open workers' compensation claims with the state of Washington reported that at 6 months significantly more SCS patients achieved leg pain relief of at least 50% on VAS compared with patients in the usual care group (N=117, 18% versus 3%; RR 5.82, 95% CI 1.32 to 25.79), but the difference between the SCS and pain clinic groups was not statistically meaningful (N=89, 18% vs. 5%; RR 3.35, 95% CI 0.77 to 14.63).[164] By 12 and 24 months, the differences were no longer statistically significant, as the control groups had improved rates of pain relief (Appendix Table F5). The authors also reported an alternative cut-off for pain relief of at least 30%; similar to the 50% cut-off 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).

4.2.1.2.1.2 Pain Scores

Low back pain (LBP)

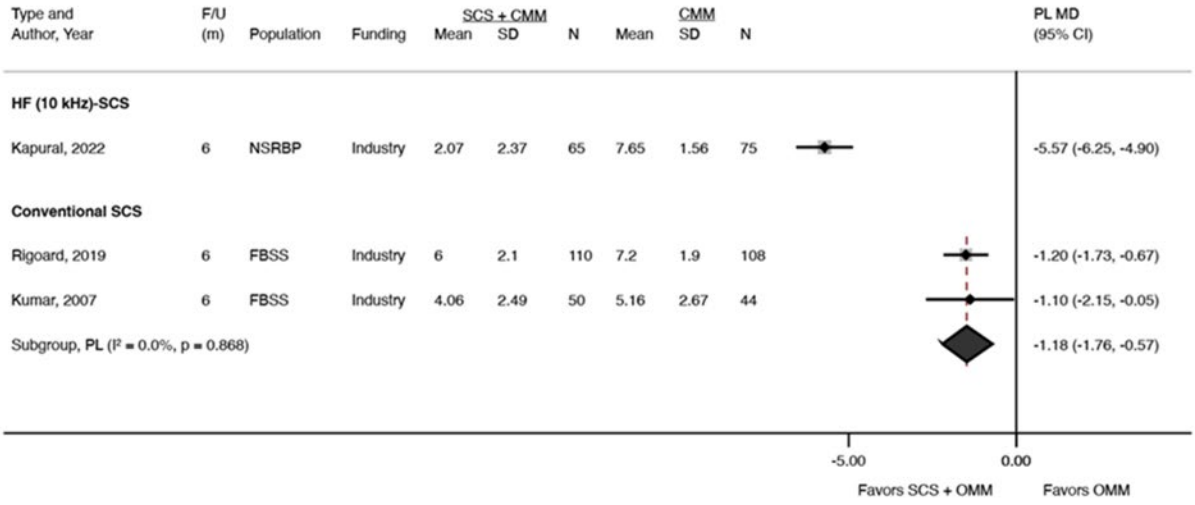
Two trials reported low back pain scores on VAS or NPRS (0-10 scale) at 3 months. HF (10 kHz)-SCS was associated with a large improvement (N=143, MD -5.31, 95% CI -5.88 to -4.75)[78] and conventional SCS

with a small improvement (N=94, MD -1.0, 95% CI -1.49 to -0.51)[92] in back pain scores compared with CMM.

Three RCTs reported low back pain scores on VAS or NPRS (0-10 scale) at 6 months (prior to crossover), Figure 4.[78,92,133] Compared with CMM alone, conventional SCS was associated with a moderate improvement in pain across two trials of patients with FBSS (ITT analysis, N=312, MD -1.18, 95% CI -1.76 to -0.57, I^2=0%)[92,133] and a large improvement in pain in one trial evaluating HF (10 kHz)-SCS in patients with NSRBP (completers analysis, N=140, MD -5.57, 95% CI -6.25 to -4.90).[78] Of note, the latter trial did not provide an ITT analysis for this outcome.

One of the trials evaluating conventional SCS for patient with FBSS also reported PP (i.e., completers) and "as treated" analyses both of which similarly favored SCS versus CMM alone (Appendix Table F2).[133]

Figure 4. Back pain scores (VAS or NPRS, 0-10 scale): SCS versus CMM for chronic back pain



CI = confidence interval; CMM = conventional medical management; FBSS = failed back surgery syndrome; F/U = follow-up; kHz = Kilohertz; m = months; MD = mean difference; NPRS = numerical pain rating scale; NSRBP = nonsurgical refractory back pain; PL = profile likelihood; SCS = spinal cord stimulation; SD = standard deviation; VAS = visual analog scale.

Two prospective comparative NRSIs reported back pain scores.[125,164] One study[164] similar improvement in back pain intensity (VAS, 0-10 scale) at 12 and 24 months between the SCS group and the usual care and pain clinic groups (Appendix Table F5). This study evaluated FBSS patients who had open workers' compensation claims with the state of Washington. Conversely, the second NRSI in patients with FBSS with radiculopathy, reported that SCS was associated with a large improvement in VAS pain intensity scores (i.e., pain at present moment scale included in the PD-Q) compared with CMM at 24 months (N=52, 0-10 scale, MD -2.05, p≤0.01).[125] Similar results were reported for the other two PD-Q VAS scales, strongest and average pain over the past month (Appendix Table F5). Authors state that SCS was superior to CMM in pain improvement at earlier timepoints as well (3, 6, 12 months) but did not provide data and the graphs were difficult to read due to poor resolution. Since the authors did not specify, we assume that these scores are evaluating back pain, as opposed to leg pain (most patients had

radiculopathy). The authors also reported PD-Q total scores (scale -1 and 38) at 24 months which, though lower (i.e., better) in the SCS group, were not statistically different compared with CMM (mean 9.3 vs. 14.08, MD -4.78, p=0.05); the PD-Q measures the quality of neuropathic pain symptoms. Authors indicate in their methods that data was adjusted for confounders (sex, age, number of previous surgeries, years since diagnosis, and symptomology).

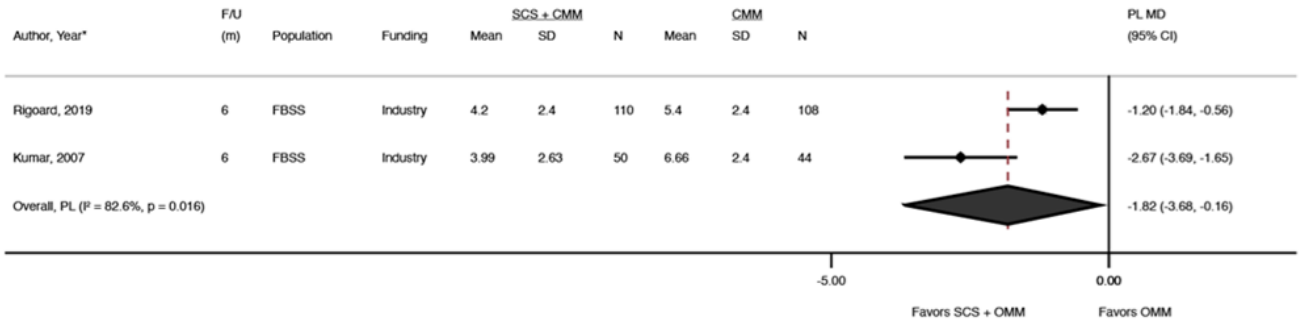
Leg pain scores

Conventional SCS was associated with a large improvement in leg pain scores on VAS (0-10) compared with CMM at 3 months in one fair-quality trial that enrolled patients with FBSS with radiculopathy and leg pain that was greater than their back pain (N=94, MD -3.30, 95% CI -3.86 to -2.73)[92]

Two RCTs that evaluated conventional SCS in patients with FBSS reported leg pain scores on VAS or NPRS (0-10 scale) at 6 months (prior to crossover).[92,133] Compared with CMM alone, conventional SCS was associated with a moderate improvement in pain in the pooled analysis according to ITT (N=312, MD -1.82, 95% CI -3.68 to -0.16, I^2=82.6%)[92,133] however, heterogeneity was substantial (Figure 5). Differences in the patient populations may explain some of the heterogeneity. One trial enrolled patients whose leg pain was less than their back pain and reported a small improvement favoring SCS (MD -1.20, 95% CI -1.84 to -0.56)[133] while the other trial included patients with radiculopathy whose leg pain was greater than their back pain and reported a large improvement in pain with SCS (MD -2.67, 95% CI -3.69 to -1.65).[92] One of the trials also reported PP (i.e., completers) and "as treated" analyses both of which similarly favored conventional SCS versus CMM alone (Appendix Table F2).[133]

The trial evaluating HF (10 kHz)-SCS for the treatment of NSRBP reported leg pain scores for the SCS group only which were comparable to the back pain scores in this group; leg pain decreased from a mean of 7.3 on VAS (0-10) at baseline to a mean of 1.5 and 1.9 at 3 and 6 months, respectively.[78]

Figure 5. Leg pain scores (VAS or NPRS, 0-10 scale): SCS versus CMM for chronic back pain



CI = confidence interval; CMM = conventional medical management; FBSS = failed back surgery syndrome; F/U = follow-up; m = months; MD = mean difference; NPRS = numerical pain rating scale; NSRBP = nonsurgical refractory back pain; PL = profile likelihood; SCS = spinal cord stimulation; SD = standard deviation; VAS = visual analog scale.
*Riogard, 2019: for inclusion, leg pain had to be less than back pain; Kumar, 2007: for inclusion, leg pain had to be greater than back pain (all patients had radiculopathy).

In addition, one prospective comparative NRSI[164] evaluating FBSS patients who had open workers' compensation claims with the state of Washington reported similar improvement in leg pain (VAS, 0-10

scale) between the SCS group and the usual care and pain clinic groups at 6, 12 and 24 months according to adjusted analyses (Appendix Table F5).

4.2.1.2.2 Function

4.2.1.2.2.1 Function Success

Only one RCT reported function "success" (responders) i.e., the proportion of patients in each group with ≥10-point reduction in ODI scores.[78] At all timepoints measured, HF (10 kHz)-SCS was associated with a substantial increase in the likelihood of achieving function response in patients treated for NRSBP (Table 11).

Table 11. Function Success/Response Based on the ODI: 10 kHz SCS versus CMM for NSRBP

Author, year	Outcome	Definition	Timing	10 kHz SCS % (n/N)	CMM % (n/N)	RR (95% CI)
Kapural, 2022 **PP analysis**	**ODI responder**	≥10 point reduction in ODI score (0-100)	1 mos.	67.7% (46/68)	8.1% (6/75)	8.45 (3.86, 18.54)
			3 mos.	80.9% (55/68)	12.0% (9/75)	6.74 (3.61, 12.58)
			6 mos.	78.5% (51/65)	4.0% (3/75)	18.75 (6.13, 57.31)

CI = confidence interval; CMM = Conventional medical management; kHz = Kilohertz; mos. = months; NSRBP = nonsurgical refractory back pain; ODI = Oswestry Disability Index; PP = Per protocol; RR = Risk ratio; SCS = Spinal cord stimulator.

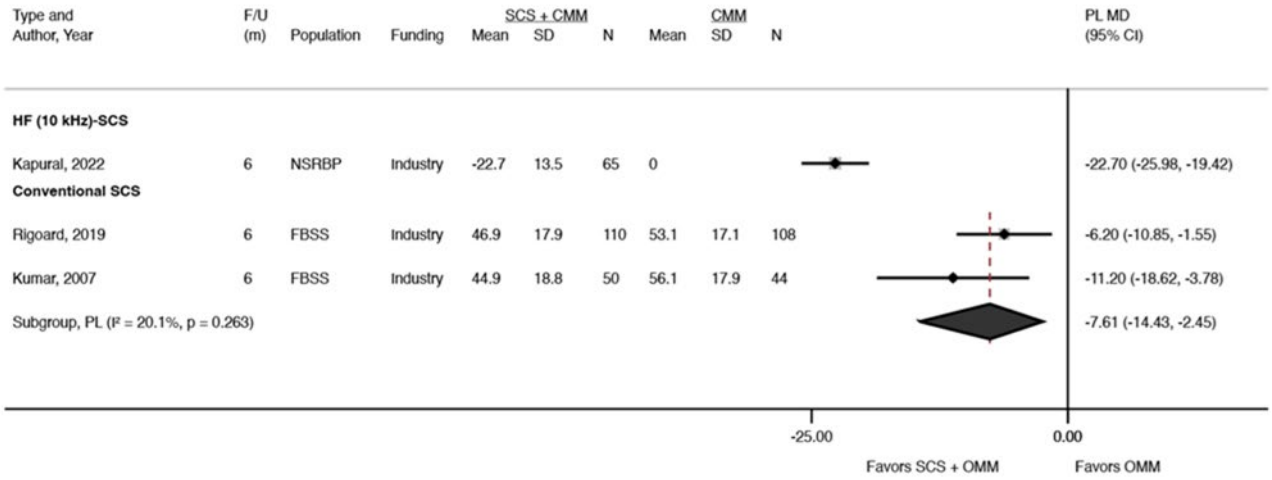
One prospective comparative NRSI[164] that evaluated FBSS patients who had open workers' compensation claims with the state of Washington reported the proportion of patients with a 2-point or greater improvement (vs. baseline) in Roland Morris Disability Questionnaire (RDQ) scores which showed similar results between SCS and the usual care or pain clinic groups at 6, 12 and 24 months (Appendix Table F5). The authors also reported alternative cut-offs for function success that they state may better represent the minimal clinically meaningful improvement for function. Using a 5-point or greater improvement in RDQ, significantly more SCS patients achieved function success at 6 months compared with both usual care (N=117, 22% vs. 5%, RR 4.75, 95% CI 1.40 to 16.12) and pain clinic (N=89, 22% vs. 5%, RR 4.10, 95% CI 0.96 to 17.42) patients. Using a 30% or greater improvement in RDQ as the criterion, significantly more SCS patients achieved success at 6 months compared with usual care (N=117, 16% vs. 3%, RR 5.18, 95% CI 1.15 to 23.33) but not compared with patients who attended pain clinic (N=89, 16% vs. 5%, RR 2.98, 95% CI 0.67 to 13.24).

4.2.1.2.2.2 Function Scores

Three RCTs reported function using the ODI (0-100) at 6 months (prior to crossover), Figure 6.[78,92,133] Compared with CMM alone, conventional SCS was associated with a small improvement in function across two trials of patients with FBSS (ITT analysis, N=312, MD -7.61, 95% CI -14.43 to -2.45, I^2=20.1%)[92,133] and a large improvement in function in one trial evaluating HF (10 kHz)-SCS in patients with NSRBP (completers analysis, N=140, MD -22.70, 95% CI -25.98 to -19.42).[78] Of note, the latter trial did not provide an ITT analysis for this outcome.

One of the trials evaluating conventional SCS in patients with FBSS also reported PP (i.e., completers) and "as treated" analyses both of which similarly favored conventional SCS versus CMM alone (Appendix F2).[133]

Figure 6. Function scores (ODI, 0-100 scale): SCS versus CMM for chronic back pain



CI = confidence interval; CMM = conventional medical management; FBSS = failed back surgery syndrome; F/U = follow-up; kHz = Kilohertz; m = months; MD = mean difference; NPRS = numerical pain rating scale; NSRBP = nonsurgical refractory back pain; PL = profile likelihood; SCS = spinal cord stimulation; SD = standard deviation; VAS = visual analog scale.

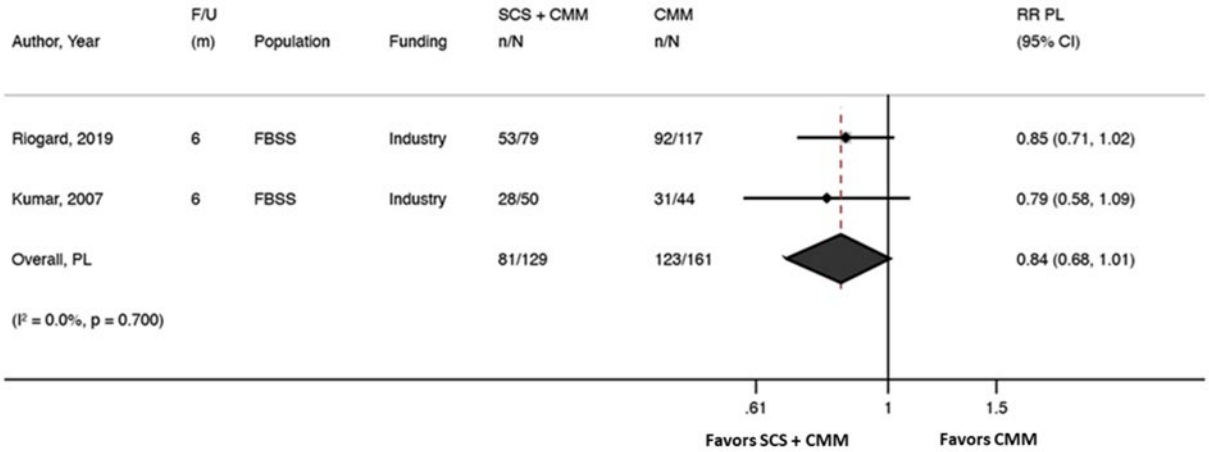
Two prospective comparative NRSIs reported function outcomes using different measures.[125,164] One NRSI[164] that evaluated FBSS patients who had open workers' compensation claims with the state of Washington reported similar improvement in RDQ scores (0-24 scale) between the SCS group and the usual care and pain clinic groups at 6, 12 and 24 months according to adjusted analyses (Appendix Table F5). Similarly, the second NRSI reported similar improvement in ODI scores (0-100 scale) at 24 months for patients with FBSS with radiculopathy treated with SCS versus CMM (Appendix Table F5).[125] Authors indicate in their methods that data was adjusted for confounders (sex, age, number of previous surgeries, years since diagnosis, and symptomology).

4.2.1.2.3 Opioid Use

4.2.1.2.3.1 Proportion of Patients Using Opioids

Across two RCTs in patients with FBSS, conventional SCS (plus CMM) was associated with a small reduction in the proportion of patients still using opioids at 6 months (prior to crossover) versus CMM alone (N=290, RR 0.84, 95% CI 0.68 to 1.01, I^2=0%), Figure 7.[92,133]

Figure 7. Proportion of patients using opioids: SCS versus CMM for chronic back pain



CI = confidence interval; CMM = conventional medical management; FBSS = failed back surgery syndrome; F/U = follow-up; m = months; PL = profile likelihood; RR = risk ratio; SCS = spinal cord stimulation.

The trial comparing HF (10 kHz)-SCS versus CMM delineated between patients who increased, decreased, or maintained a stable dosage of opioids or who stopped opioid all together up to the 6 month follow-up (Appendix Table F2).[78] According to the PP analysis (i.e., completers, N=140), HF SCS was associated with a substantially better outcomes: more patients decreased opioid use (44% vs. 17%, RR 2.40, 95% CI 1.35 to 4.25) or stopped altogether (22% vs. 0%) and fewer patients increased opioid use (6% vs. 49%, RR 0.12, 95% CI 0.05 to 0.33) compared with CMM. A similar proportion of patients in both groups remained on the same dose of opioids (28% vs. 34%).

In addition to the RCTs, four comparative NRSIs reported on opioid use in patients with FBSS who had received SCS versus CMM (or no SCS) only with varying results.[37,125,164,177]

Both prospective comparative NRSIs, one in FBSS patients who had open workers' compensation claims with the state of Washington (N=158)[164] and one in FBSS patients with radiculopathy,[125] reported similar proportions of patients using opioids for back/leg pain through 24 months in the SCS groups and control groups (usual care and pain clinic groups in one study and CMM in one study) (Appendix Table F5).

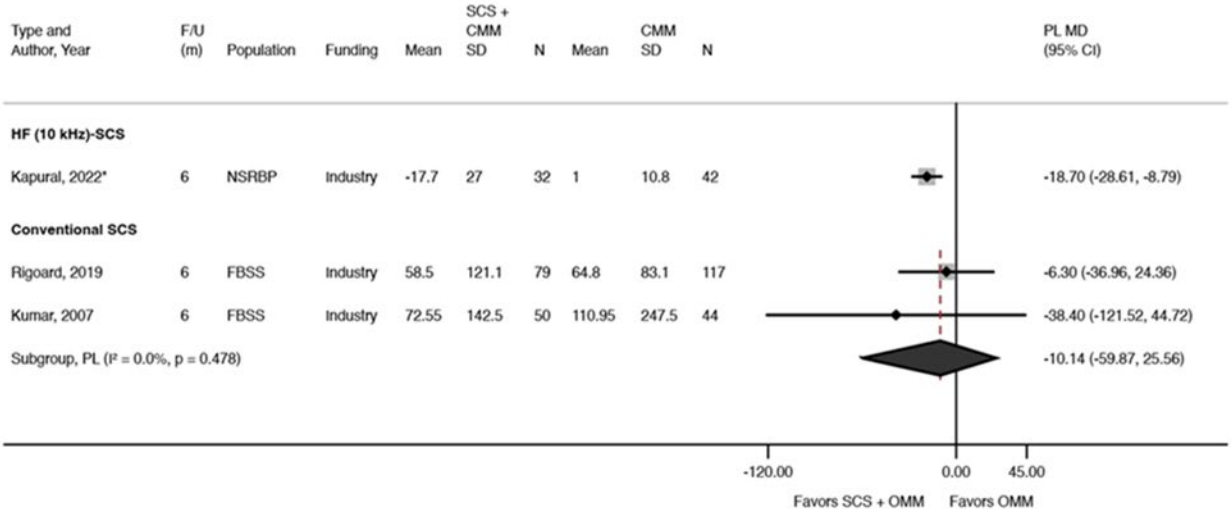
The other two NRSIs were large retrospective database studies (Optum Labs Data Warehouse and TriNetx Diamond Network) that conducted propensity score matched analyses. In one study,[177] SCS was associated with a significant, but not a clinically meaningful, reduction in long-term opioid therapy across all definitions compared with no SCS through 15 months: ≥6 prescriptions/year (primarily analysis) (OR 0.93, 95% CI to 0.87 to 0.98), ≥10 prescriptions/year (OR 0.93, 95% CI 0.87 to 0.98), and ≥4 prescriptions per year (OR 0.94, 95% CI 0.89 to 1.00); all estimates failed to meet our cut-off for a small effect (OR >0.83). Similarly, among opioid-naive patients, SCS was also associated with a statistically significant decrease in the odds of starting opioids across all definitions of long-term opioid use compared with no SCS through 15 months but again, the effect estimates did not meet our clinically meaningful cut-off (Appendix Table F5). The second study (N=7,560)[37] evaluated patients with mixed, but primarily FBSS (71%), diagnoses (other: 26% chronic pain not otherwise specified, 10% CRPS, 1% other chronic back/extremity pain) and found that SCS was associated with a higher likelihood of chronic

opioid use (54.9% vs. 51.8%; adjusted odds ratio [aOR], 1.14, 95% CI 1.01 to 1.29), long-acting opioid use (22.5% vs. 18.5%; aOR 1.28; 95% CI 1.11 to 1.49) and high MME dose (64.7% vs. 50.3%, aOR 1.81, 95% CI 1.60 to 2.04) compared with CMM through 12 months follow-up. However, only the likelihood of long-acting opioid use and high MME dose were clinically meaningful showing a small and moderate effect, respectively; the estimate for chronic opioid use did not meet our threshold for a small effect (OR >0.83). After 12 months and up to 24 months both treatment groups showed similar results on all measures of opioid use (Appendix Table F5). The authors also reported that among patients with at least one opioid prescription fill during the 6-month baseline period, SCS was associated with a significantly (large effect) lower rate of opioid discontinuation compared with CMM (N=5,854; 2.1% vs. 5.9%, RR 0.36, 0.23 to 0.56) over the entire 24-month follow-up period, especially during the first 12 months (3.1% vs. 10.0%, RR 0.31, 95% CI 0.22 to 0.45); 13 to 24 months: 17.1 % vs. 18.0%, p=0.47).

4.2.1.2.3.2 Morphine Milligram Equivalents (MME) dosage

Three RCTs reported opioid use in terms of MME dosage (mg) at 6 months (prior to crossover), Figure 8.[78,92,133] Opioid dosage was similar between conventional SCS (plus CMM) and CMM alone across two trials in patients with FBSS (N=290, MD -10.14, 95% CI -59.87 to 25.56, I^2=0%).[92,133] One trial reported MME dosage for the population as treated[133] while the other reported it for the ITT population.[92] In the trial comparing HF (10 kHz)-SCS versus CMM alone in patients with NSRBP, SCS was associated with a reduction in opioid dosage among patients using opioids at baseline (N=74, MD -18.70, 95% CI -28.61 to -8.79).[78]

Figure 8. Mean opioid use (MME dose): SCS versus CMM for chronic back pain



CI = Confidence interval; CMM = Conventional medical management; FBSS = Failed back surgery syndrome; F/U = Follow-up; HF = High frequency; kHz = Kilohertz; m = months; MD = Mean difference; MME = Morphine milligram equivalents; NSRBP = nonsurgical refractory back pain; PL = Profile likelihood; SCS = Spinal cord stimulation; SD = Standard deviation.
* The denominator for Kapural, 2022 for proportion of patients using opioids appears to be those who were using opioids at baseline.

4.2.1.2.4 Secondary Outcomes

4.2.1.2.4.1 Quality of Life

EQ-5D index and VAS scores

Three fair-quality trials reported EQ-5D index scores (scale -0.2241 to 1) (Appendix Table F12). At 3 months, SCS was associated with significantly better quality of life scores compared with CMM across two RCTs, one evaluating 10 kHz SCS (MD 0.23, 95% CI 0.19 to 0.27)[78] and one evaluating conventional SCS (adjusted MD 0.27, 95% CI 0.15 to 0.39).[99] These results persisted to 6 months across all three RCTs: 10 kHz SCS (MD 0.26, 95% CI 0.23 to 0.29)[78] and conventional SCS (MD 0.11, 95% CI 0.03 to 0.19 and adjusted MD 0.23, 95% CI 0.12 to 0.35).[99,133]

One of these trials also reported EQ-5D overall health VAS scores at 6 months in the as-treated population only[133]; the authors reported a significant difference favoring conventional SCS compared with CMM alone in change scores from baseline (MD 10.4, 95% CI 3.2 to 17.7) but results were similar between groups for follow-up scores according to our calculations (MD 4.00, 95% CI -2.76 to 10.76) (Appendix Table F12)

Additionally, one prosective comparative NRSI (N=53) reported that SCS was associated with significant improvement in EQ-5D index scores (MD 0.29, p≤0.01) and EQ-VAS scores (MD 19.17, p≤0.01) at 24 months compared with CMM for the treatment of FBSS with radiculopathy (Appendix Table F5).[125] Authors indicate in their methods that data was adjusted for confounders (sex, age, number of previous surgeries, years since diagnosis, and symptomology).

SF-36 scores

One trial reported SF-36 PCS and MCS scores (0-100) at 6 months (Appendix Table F12).[133] According to ITT analysis, conventional SCS was associated with improvement in SF-36 folow-up scores compared with CMM alone (MD 3.76, 95% CI 1.53 to 5.99), however the difference was below the threshold for a small effect. The results were comparable in the completeres (PP) analysis. SF-36 MCS scores at 6 months were similar between groups in the as-treated analysis (the only analysis reported for this outcome).

In addition, one prospective NRSI[164] reported similar SF-36 mental health scores between the SCS group and the usual care and pain clinic groups at 12 and 24 months (Appendix Table F5).

4.2.1.2.4.2 Depression and Anxiety

One prosective comparative NRSI reported similar Hospital Anxiety and Depression Scale (HADS) depression, anxiety and global scores at 24 months between patients treated with SCS versus CMM for FBSS with radiculopathy (Appendix Table F5).[125] Authors indicate in their methods that data was adjusted for confounders (sex, age, number of previous surgeries, years since diagnosis, and symptomology).

4.2.1.2.4.3 Patient Satisfaction

Two trials evaluting conventional SCS reported higher rates of patients satisfaction with their pain relief at 6 months (moderate to large effects).[92,133] Additionally, more patients who received SCS reported that they would choose the same treatment again compared with those who received CMM in one of these trials.[92] (Appendix Table F13)

4.2.1.2.4.4 Global Impression of Change

HF (10 kHz)-SCS was asscoiated with a substanially greater likelihood that patients rated themselves as better or a great deal better on the patient global impression of change scale according to the PP (completers) analysis: 70.8% vs. 1.3% (RR 53.08, 95% CI 7.53 to 374.24); however the effect estimate was very imprecise (Appendix Table F13).[78]

4.2.1.3 SCS vs. Reoperation: Parallel RCTs

One parallel RCT (N=60, mean age 52 years, 52% female) compared conventional SCS versus reoperation for the treatment of FBSS.[119] Details regarding study inclusion and exclusion criteria can be found in Appendix Table G12. The average number of prior back surgeries was 2.5. All individuals had failed CMM prior to inclusion. Average symptom duration and opioid use at baseline, and comorbidities were not reported. The SCS trial implantation period was a minimum of 3 days (mean not reported) and 79 percent of participants experienced a successful trial leading to permanent implantation of the Xtrel of Itrel generator and Resume electrode. It should be noted that the device used during the trial period was not the same as the permanently implanted SCS device. Appendix Table G8 below provides details regarding SCS trial success criteria and SCS and reoperation treatment parameters. Participants in the SCS arm were allowed to crossover and receive reoperation upon trial failure (21% crossed over). At six months, participants in the reoperation arm were allowed to crossover and receive SCS treatment (54% crossed over). This trial was conducted at a single site in the U.S., was industry-funded, and authors had industry-based conflicts of interest. This trial was considered fair quality, the primary limitations being lack of blinding and differential attrition between the groups (see Appendix E for details on study quality).

4.2.1.3.1 Treatment “Success”

Treatment “success” was defined as pain relief ≥50% (the outcome measure used to measure pain was not disclosed) and patient satisfaction (would you go through the treatment again given your experience so far). According to ITT analysis, SCS was associated with a large increase in the likelihood of acheiving treatment success compared with reoperation at long-term (mean 2.9 years) follow-up: 47% (9/19) versus 12% (3/26), RR 4.11 (95% CI 1.28 to 13.16).[119] The results from several additional analyses (worst-case analysis [those lost to follow-up were failures], per-protocol analysis [analyzed by treatment received at final follow-up] and treated as randomized versus crossovers) resulted in similar conclusions (Appendix Table F2).

4.2.1.3.2 Opioid Use

Significantly more patients in the SCS group were taking a stable or decreased dose of opioid medications compared with baseline versus those in the reoperation group (87% [20/23] vs. 58% [15/26], RR 1.51, 95% CI 1.05 to 2.17) at final follow-up (mean 2.9 years)[119]; the effect size was moderate. Medication dosages were not reported.

In addition, one large retrospective database (MarketScan) study (N=6,497)[97] conducted a propensity score matched analysis (N=111 in each group) comparing patients who had undergone SCS versus lumbar reopertion for the treatment of FBSS. The proportion of patients using opioids at 12 months (66.7% vs. 65.8%) and 24 months (71.2.% vs. 66.7%) as well as the number of prescriptions mediations (not specific to opioids) filled over the 24 month follow-up was similar between groups (Appendix Table F5).

4.2.1.3.3 Other Outcomes

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 (mean 2.9 years), however, raw data were not provided.[119]

4.2.2 Painful Diabetic Neuropathy: Parallel RCTs

Three RCTs (in 7 publications) that met inclusion criteria compared SCS in addition to CMM with CMM alone for the treatment of painful diabetic neuropathy (PDN).[33,39,126-128,147,167] Two trials evaluated conventional SCS[33,147] and one evaluated HF (10 kHz) SCS.[127] Details regarding study inclusion and exclusion criteria can be found in Appendix Table G12. The patient populations across these trials were similar and are described together below; however, given some of the inherent differences between conventional and HF SCS, results are reported separately by type of intervention.

Appendix Table G9 provides an overview of patient and study characteristics across the three RCTs. Sample sizes ranged from 36 to 216 (Total N=312). The average age of participants was 60 years (range, 57 to 61), 37 percent were female (range, 33% to 37%) and most had type II diabetes (90%; range, 75% to 95%). All patients had moderate to severe pain in the lower extremities with an average symptom duration of 7 years (range, 5.6 to 7.3 years). Almost half of participant were using opioids at study entry across two RCTs, 48% in one conventional SCS trial[33] and 44% in the HF SCS trial[127]; the HF-SCS trial excluded patients with a daily opioid dosage greater than 120 mg morphine equivalents however. The other conventional SCS trial[147] only indicated that pain medications were being used by some participants at baseline. Prior surgery and comorbidities were not reported although all trials excluded participants with coagulation disorders and psychiatric problems significant enough to interfere with treatment.

SCS trial periods ranged from 7 to 14 days across the conventional SCS trials and 5 to 7 days in the HF SCS trial and 87 percent (range, 77% to 93%) of participants experienced a successful trial leading to permanent SCS device implantation. Appendix Table G9 provides details regarding SCS trial success criteria and SCS and CMM treatment parameters. Across all trials, CMM was not standardized, was provided at the treating physicians discretion, and could include a wide variety of treatment modalities.

Follow-up periods ranged from 6 to 24 months across the two conventional SCS trials[33,147] and was 12 months in the HF SCS trial.[127] In all trials, patients with inadequate pain relief or who were unsatisfied with their treatment could cross over to the other treatment after 6 months with most patients in the CMM group opting to receive SCS (75% to 93%). Given the high frequency of crossover, our results focus on the 6-month timepoint, prior to crossover; information regarding longer term outcomes in SCS patients can be found in Appendix Table F3. In general, the trials indicated that the improvements seen with SCS during the first 6 months were sustained longer term.

The two trials that evaluated conventional SCS were conducted in Europe; one across multiple countries (Netherland, Denmark, Belgium, Germany)[33] and the other in the Netherlands.[147] The trial evaluating HF SCS was conducted across 18 U.S. sites (academic centers and independent pain clinics). All RCTs were industry funded and had authors with industry-based conflicts of interest. All three trials were rated fair quality with the biggest limitation being the inability to blind providers and patients (who were also outcome assessors given the self-report nature of the outcomes). Allocation concealment was also not adequately described. In addition, there was differential loss to follow-up between groups in the HF SCS trial (greater attrition in the SCS group).[127] See Appendix E for details on study quality.

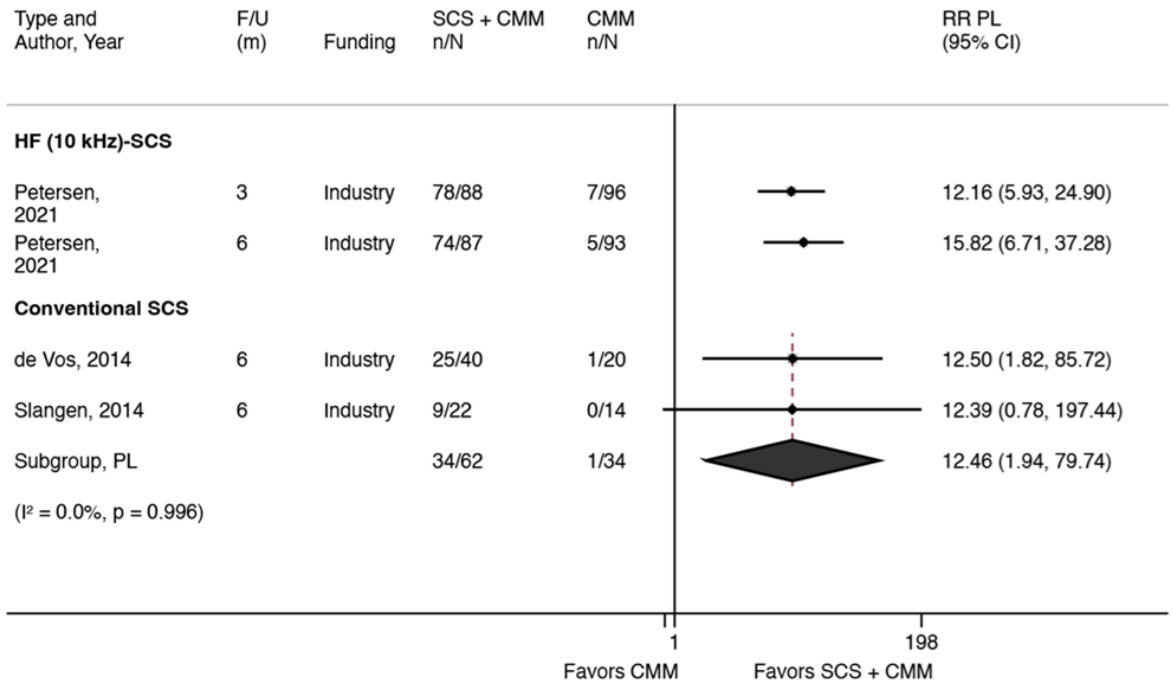
Given some of the inherent differences between conventional and HF (10 kHz) SCS, results are reported separately by type of intervention. Also, given the high frequency of crossover, the results that follow focus on the 6-month timepoint, prior to crossover; information regarding longer term outcomes in SCS patients can be found in Appendix Tables F3 and F7 for the two trials that reported data at later timepoints.[127,147] These data are not comparative and are essentially case series of SCS. In general, the trials indicated that the improvements seen with SCS during the first 6 months were sustained longer term i.e., out to 24 months in one trial of HF (10 kHz) SCS [126,128] and one trial of conventional SCS.[167] The HF (10 kHz) SCS trial also presented data for the CMM patients who crossed over to receive SCS and reported significant improvement in pain, neurological and quality of life outcomes through 24 months in this group, similar to those who were originally randomized to SCS.

4.2.2.1 Pain

4.2.2.1.1 Pain Responders

Three fair-quality RCTs, two evaluating conventional SCS and one evaluating HF (10 kHz)-SCS, reported pain "success" (responders) i.e., the proportion of patients in each group with ≥50% reduction in lower extremity (LE) pain on the VAS or the NRS (0-10).[33,127,147] SCS (in addition to CMM) was associated with a large increase in the likelihood of achieving pain response compared with CMM alone at 3 months (N=184, 88.6% vs. 7.3%, RR 12.16, 95% CI 5.93 to 24.90) and 6 months (N=180, 85.1% vs. 5.4%, RR 15.82, 95% CI 6.71 to 37.28) in the trial evaluating 10 kHz SCS[127] and at 6 months across the two trials evaluating conventional SCS (N=96, 54.8% vs. 2.9%, RR 12.46, 95% CI 1.94 to 79.74, I^2=0%) (Figure 9); however, estimates were imprecise. Both trials evaluating conventional SCS used ITT analyses for reporting; the trial evaluating HF (10 kHz)-SCS used completers/per protocol analysis.

Figure 9. Lower Extremity Pain Responders (≥50% reduction on VAS or NRS): SCS versus CMM for PDN



CI = Confidence interval; CMM = Conventional medical management; F/U = Follow-up; HF = High frequency; kHz = Kilohertz; m = months; PL = Profile likelihood; RR = Risk ratio; SCS = Spinal cord stimulation; SD = Standard deviation.

The trial that evaluated HF (10 kHz)-SCS also reported several other "responder" outcomes to include a composite outcome that includes pain and neurological assessment (authors' primary outcome), pain response using an alternative definition to the one above, remission, clinically confirmed PDN and overall improvement on neurological assessment (Table 12); in all cases, SCS was associated with significantly better outcomes compared with CMM.[127]

Table 12. Summary of Other Responder Outcomes Reported by Petersen et al. trial comparing 10 kHz SCS versus CMM for PDN

Author, year	Outcome	Definition	F/U	10 kHz SCS % (n/N)	CMM % (n/N)	RR (95% CI)	ES favoring SCS
Petersen, 2021 **SENZA-PDN trial** **PP analyses**	Composite, authors' 1° outcome – ITT analysis	≥50% reduction in (LE) pain on the VAS without deterioration on neurological exam	6 mos.	78.9% (75/95)	5.3% (5/94)	14.84 (6.29, 35.05)	Large
	Composite, authors' 1° outcome – PP analysis		6 mos.	86.2% (75/87)	5.3% (5/94)	16.21 (6.88, 38.19)	Large
	Pain "Success"/ Responder	LE pain on VAS ≤3	3 mos.	78.4% (69/88)	5.2% (5/96)	15.05 (9.69, 23.37)	Large
			6 mos.*	86% (76/88)	5.2% (5/96)	16.58 (10.68, 25.74)	Large

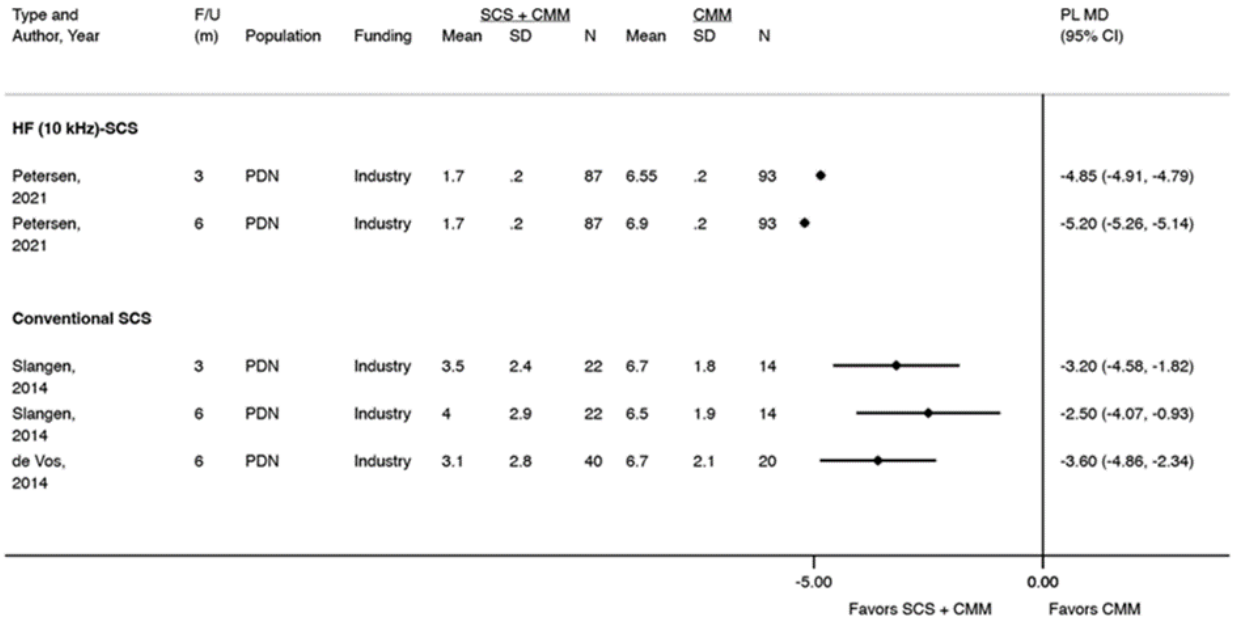
	Remitter/ Remission	LE pain on VAS ≤3 for 6 consecutive months	6 mos.	60.2% (53/88)	1.1% (1/95)	57.22 (21.05, 155.54)	Large
	Clinically confirmed PDN	DN4 score ≥3	3 mos.*	66.5% (56/84)	95.6% (87/91)	0.7 (0.65, 0.76)	Small
			6 mos.	64.3% (54/84)	95.6% (87/91)	0.67 (0.62, 0.73)	Moderate
	Overall improvement on neurological assessment	No deficit (vs. baseline) in any motor, sensory, or reflex outcomes and improvement in ≥1 outcome	3 mos.	72.4% (63/87)	6.4% (6/94)	11.34 (7.6, 16.92)	Large
			6 mos.	61.9% (52/84)	3.3% (3/92)	18.98 (10.73, 33.56)	Large

CI = confidence interval; CMM = conventional medical management; DN4 = Douleur Neuropathique score; ES = effect size; LE = lower extremity; mos. = months; PDN = painful diabetic neuropathy; PP = per protocol/completers analysis; RR = Risk ratio; SCS = spinal cord stimulation; VAS = visual analog scale.
*Percentages were estimated from graphs in article and numerators were back calculated using the denominators provided.

4.2.2.1.2 Pain Scores

Three fair-quality RCTs, two evaluating conventional SCS and one evaluating HF (10 kHz)-SCS, reported LE pain scores on VAS or NRS (0-10 scale).[33,127,147] Both types of SCS (in addition to CMM) were associated with a large improvement in pain scores compared with CMM alone at 3 months (1 HF-SCS trial: MD -4.85, 95% CI -4.91 to -4.79[127] and 1 conventional SCS trial: MD -3.20, 95% CI -4.58 to -1.82[147]) and at 6 months in the HF-SCS trial (MD -5.20, 95% CI -5.26 to -5.14) and across the two conventional SCS trials (N=96, MD -3.17, 95% CI -4.49 to -1.66, I^2=12.7%) (Figure 10). The HF SCS trial reported per protocol analysis (completers) only and the two conventional SCS trials reported ITT analyses.

Figure 10. LE pain scores (VAS or NRS, 0-10 scale): SCS versus CMM for PDN



CI = Confidence interval; CMM = Conventional medical management; F/U = Follow-up; HF = High frequency; kHz = Kilohertz; LE = lower extremity; m = months; MD = Mean difference; NRS = Numerical rating scale; PDN = Painful diabetic neuropathy; PL = Profile likelihood; SCS = Spinal cord stimulation; SD = Standard deviation; VAS = Visual analog scale.

All three trials reported various other measures of pain to include DN4 and SF-MPQ-2 scores (1 RCT, 10 kHz SCS),[127] mBPI-DPN PSI and PII scores and NPS scores (1 RCT, conventional SCS)[147] and SF-MPQ PRI-T and NWC-T scale scores (1 RCT, conventional SCS).[33] In all cases, SCS (both 10 kHz and conventional) was associated with significant (typically large) improvement in pain compared with CMM alone (Table 13). The trial evaluating HF (10 kHz)-SCS reported these results using a per-protocol or completers analysis only[127]; the two trials of conventional SCS reported ITT analyses.[33,147]

Table 13. Summary of other continuous pain measures reported by PDN trials comparing SCS versus CMM

Author, year	Outcome	Timing	SCS* Mean (SD)	CMM Mean (SD)	MD (95% CI)	ES favoring SCS
Petersen, 2021 SENZA-PDN trial **10 kHz SCS** **PP analyses**	DN4 score (0-10, worst)	6 mos.	3.5 (95% CI 3.2 to 3.8) (n=84)	6.5 (95% CI 6.3 to 6.7) (n=91)	-3 (-3.18, -2.82)	Large
	SF-MPQ-2 Total† (0-10, worst)	6 mos.	1.7 (95% CI 1.3 to 2.0) (n=87)	5.4 (95% CI 4.9 to 5.9) (n=93)	-3.7 (-4.01, -3.39)	Large
Slangen, 2014	mBPI-DPN – PSI (0-10, worst)	3 mos.	4.0 (2.5) (n=22)	6.1 (1.8) (n=14)	-2.1 (-2.82, -1.38)	Large
		6 mos.	4.0 (2.8) (n=22)	6.5 (2.1) (n=14)	-2.5 (-8.14, -3.14)	Large
		3 mos.	3.0 (2.1) (n=22)	5.6 (1.8) (n=14)	-2.6 (-3.26, -1.94)	Large

Conventional SCS **ITT analyses**	mBPI-DPN – PII (0-10, worst)	6 mos.	3.5 (2.6) (n=22)	5.5 (1.6) (n=14)	-2 (-2.7, -1.3)	Large
	NPS – Intensity‡ (0-10, worst)	3 mos.	4.5 (2.8) (n=22)	7.3 (1.6) (n=14)	-2.8 (-3.53, -2.07)	Large
		6 mos.	4.3 (3.0) (n=22)	7.3 (2.0) (n=14)	-3 (-3.83, -2.17)	Large
	NPS – Unpleasant-ness‡ (0-10, worst)	3 mos.	5.1 (2.9) (n=22)	7.2 (1.7) (n=14)	-2.1 (-2.87, -1.33)	Large
		6 mos.	5.4 (2.8) (n=22)	7.5 (1.6) (n=14)	-2.1 (-2.83, -1.37)	Large
de Vos, 2014 **Conventional SCS** **ITT analyses**	SF-MPQ PRI-T (scale NR)	6 mos.	15 (14) (n=40)	26 (10) (n=20)	-11 (-14.65, -7.35)	Unclear
	SF-MPQ NWC-T (scale NR)	6 mos.	8 (7) (n=40)	13 (4) (n=20)	-5 (-8.11, -1.89)	Unclear

CMM = conventional medical management; CI = confidence interval; DN4 = Douleur Neuropathique score; ITT = intentional-to-treat; mBPI-DPN – PII = modified Brief Pain Inventory for Diabetic Peripheral Neuropathy, Pain Interference Index; mBPI-DPN – PSI = modified Brief Pain Inventory for Diabetic Peripheral Neuropathy, Pain Severity Index; MD = mean difference; mos. = months; NPS = Neuropathic Pain Scale; PDN = painful diabetic neuropathy; NWC-T = total number of words chosen (from the SF-MPQ); PP = per-protocol or completers analysis; PRI = Pain Rating Index (SF-MPQ); SCS = spinal cord stimulation; SD = standard deviation; SF-MPQ = Short Form McGill Pain Questionnaire 2.
* SCS was in addition to CMM in all trials.
† Total is comprised of subscales for continuous pain, intermittent pain, neuropathic pain and affective descriptors. SCS was superior to CMM on all subscales.
‡ NPS includes two items that assess the global dimensions of pain intensity and unpleasantness and eight items that assess the specific qualities of neuropathic pain (deep pain, surface pain, coldness, hotness, dullness, sharpness, sensitivity, itching). Except for coldness and itching at 3 months, all other scales favored SCS at all timepoints.

4.2.2.2 Function

None of the trials reported function outcomes.

4.2.2.3 Opioid use

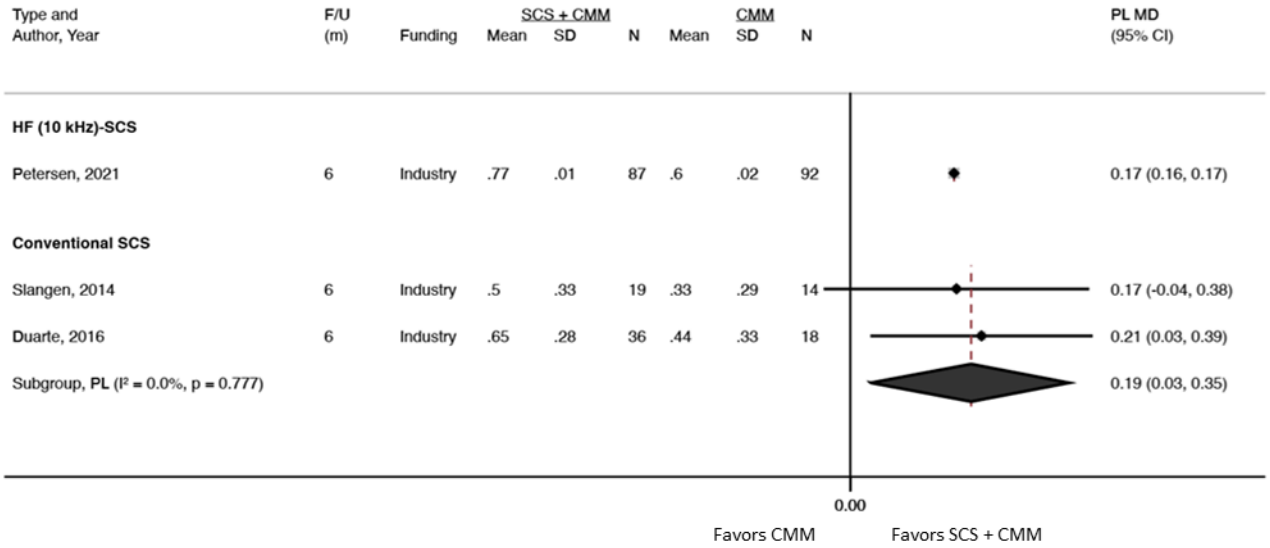
One small fair-quality trial reported that fewer patients who received conventional SCS were taking opioids at 6 months compared with those who received CMM alone according to ITT analysis (N=60, 38% vs. 55%, RR 0.68, 95% CI 0.39 to 1.20) however the difference was not statistically significant[33]; in the SCS group, three patients (of 18 using opioids at baseline) discontinued opioid use completely by 6 months compared with no patient in the CMM alone group (all 11 patients using opioids at baseline still used opioids). This same trial also reported the Medication Quantification Scale III (MQS III) which is calculated by multiplying a score for the used analgesic dosage by the detriment weight for its given pharmacological class and summing all values to get a total score. At 6 months, MQS III scores were similar between the two groups (MD -2.4, 95% CI -7.08 to 2.28); however, the conventional SCS group reduced their scores by a mean of 2.9 points compared with baseline while the CMM group's mean score increased 0.9 points. A second small trial (N=36) that also evaluated conventional SCS did not report opioid use specifically but indicated that 32% of SCS patients reduced their pain medication (2 patients, 9%, stopped medication completely) compared to 0% in the CMM only group (4 patients, 29%, reported an increase in medication use).[147]

4.2.2.4 Secondary outcomes

Quality of Life (QoL)

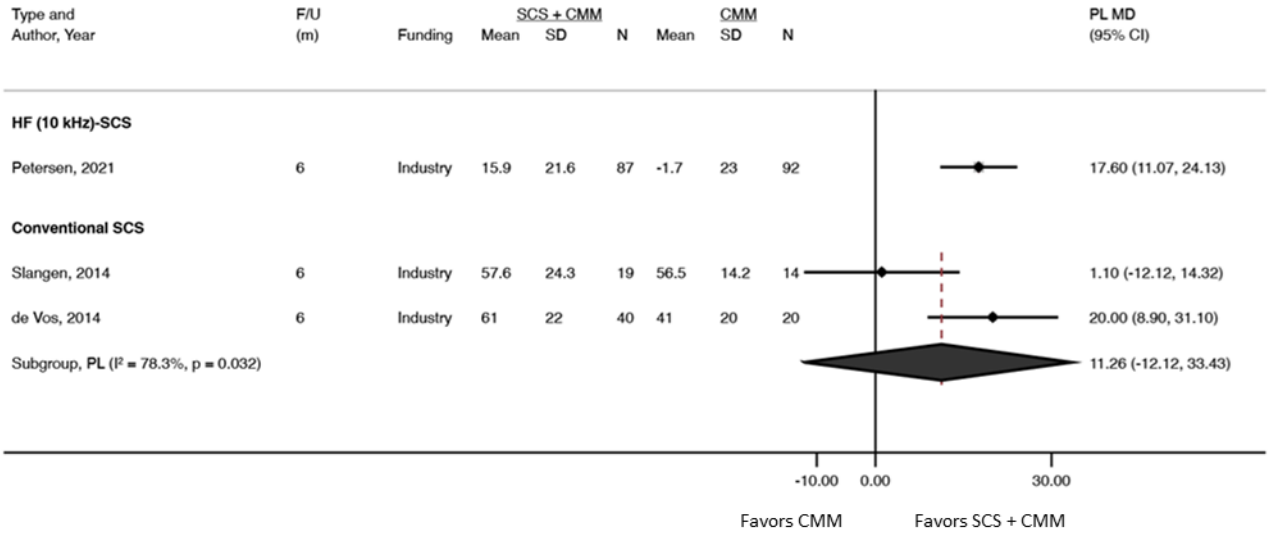
Three fair-quality RCTs reported QoL using the EQ-5D index score (scale -0.224 to 1) (Figure 11) and EQ-5D overall health VAS scale (0-100) (Figure 12) at 6 months (prior to crossover). The trial (N=172) that compared HF (10 kHz)-SCS versus CMM alone reported that SCS was associated with a moderate improvement on both measures at 6 months: EQ-5D index (MD 0.17, 95% CI 0.16 to 0.17) and EQ-5D VAS (MD 17.60, 95% CI 11.07 to 24.13).[127] In pooled analyses across the other two trials at 6 months, conventional SCS was associated with a moderate improvement in EQ-5D index scores (N=87, MD 0.19, 95% CI 0.03 to 0.35, I^2=0%)[39,147] but results were similar between groups on the EQ-5D VAS (N=93, MD 11.26, 95% CI -12.12 to 33.43, I^2=78.3%).[33,147] For the latter outcome, one trial (N=60) reported a moderate improvement with SCS (N=60, MD 20.0, 95% CI 8.90 to 31.10)[33] while the other trial found similar improvement in both groups (N=33, MD 1.10 to -12.12 to 14.32).[147] One of these trials (N=33)[147] also reported results at 3 months; SCS associated with improvement in QoL according the EQ-5D index scores but not the VAS scores (Table 14).

Figure 11. EQ-5D index scores (-0.224 to 1 scale): SCS versus CMM for PDN



CI = Confidence interval; CMM = Conventional medical management; F/U = Follow-up; HF = High frequency; kHz = Kilohertz; m = months; MD = Mean difference; PL = Profile likelihood; SCS = Spinal cord stimulation; SD = Standard deviation.

Figure 12. EQ-5D VAS for overall health scores (0-100): SCS versus CMM for PDN



CI = Confidence interval; CMM = Conventional medical management; F/U = Follow-up; HF = High frequency; kHz = Kilohertz; m = months; MD = Mean difference; PL = Profile likelihood; SCS = Spinal cord stimulation; SD = Standard deviation.

Other QoL outcomes were reported by two trials evaluating conventional SCS. One small trial (N=33)[147] reported SF-36 PCS and MCS scores at 3 and 6 months; only MCS scores at 3 months were statistically different between the groups with a small improvement favoring SCS versus CMM alone (Table 14). The second trial (N=60)[33] reported a large improvement in MPQ-QoL scores at 6 months in the SCS group versus the CMM group (Table 14).

Table 14. Summary of secondary outcomes reported by PDN trials: Quality of Life

Author, year	Outcome	Timing	Conv. SCS Mean (SD)	CMM Mean (SD)	MD (95% CI)	ES favoring SCS
Slangen, 2014 *ITT analyses*	EQ-5D-5L health VAS (0-100, best)	3 mos.	63.2 (17.4) (n=19)	58.8 (13.0) (n=14)	4.4 (-0.89, 9.69)	Similar
	EQ-5D-5L index (-0.224 to 1, best)	3 mos.	0.54 (0.32) (n=19)	0.41 (0.30) (n=14)	**0.13 (0.02, 0.24)**	**Small**
	SF-36 PCS (0-100, best)	3 mos.	33.2 (9.6) (n=19)	32.9 (6.6) (n=19)	0.3 (-2.52, 3.12)	Similar
		6 mos.	32.3 (10.5) (n=19)	30.5 (7.4) (n=14)	1.8 (-1.32, 4.92)	Similar
	SF-36 MCS (0-100, best)	3 mos.	51.4 (10.5) (n=19)	44.9 (12.4) (n=14)	**6.5 (2.4, 10.6)**	**Small**
		6 mos.	49.3 (11.5) (n=19)	46.7 (12.0) (n=14)	2.6 (-1.55, 6.75)	Similar
de Vos, 2014 *ITT analyses*	MPQ – QoL score (0-27, worst)	6 mos.	8 (7) (n=40)	14 (6) (n=20)	**-6 (-7.74, -4.26)**	**Large**

CI = confidence interval; CMM = conventional medical management; Conv. = conventional; EQ-5D-5L = EuroQol 5 dimensions questionnaire; ES = effect size; ITT = intention-to-treat; MCS = Mental Component Score; MD = mean difference; mos. = months; MPQ = McGill Pain Questionnaire; PCS = Physical Component Score; PDN = painful diabetic neuropathy; QoL = quality of life; SCS = Spinal cord stimulation; SD = standard deviation; SF-36 = Short Form 36 quality of life questionnaire.

Mental Health outcomes

Two trials reported outcomes related to mental health (Table 15). HF (10 kHz)-SCS was associated with improvement in psychological, social, and occupational functioning compared with CMM as measured by the Global Assessment of Functioning scale at 3 and 6 months.[127] There was no difference in Beck Depression Inventory scores between conventional SCS and CMM at either timepoints in the other trial.[147]

Table 15. Summary of secondary outcomes reported by PDN trials: Mental Health

Author, year	Outcome	Timing	SCS Mean (95% CI or SD)	CMM Mean (95% CI or SD)	MD (95% CI)	ES favoring SCS
Petersen, 2021 SENZA-PDN trial **10 kHz SCS** **PP analyses**	Global Assessment of Functioning (0-100, best)*	3 mos.	79.5 (76.5 to 82.5) (n=86)	61.5 (57 to 64) (n=91)	**18 (15.65, 20.35)**	Moderate
		6 mos.	80.7 (77.7 to 83.7) (n=86)	59 (55 to 62) (n=91)	**21.7 (19.35, 24.05)**	Large
Slangen, 2014 **Conventional SCS** **ITT analyses**	Beck Depression Inventory (0-63, worse)	3 mos.	12.1 (9.0) (n=19)	12.7 (5.2) (n=14)	**-0.6 (-3.09, 1.89)**	Similar
		6 mos.	13.0 (9.8) (n=19)	14.4 (6.3) (n=14)	**-1.4 (-4.21, 1.41)**	Similar

CI = Confidence interval; CMM = Conventional medical management; ES = Effect size; ITT = Intention-to-treat; kHz = Kilohertz; MMD = Mean difference; mos. = months; PDN = Painful diabetic neuropathy; PP = Per protocol; SCS = Spinal cord stimulation; SD = Standard deviation.
*Scores estimated from graph. Physician's evaluation of how much a patient's symptoms affect psychological, social, and occupational functioning.

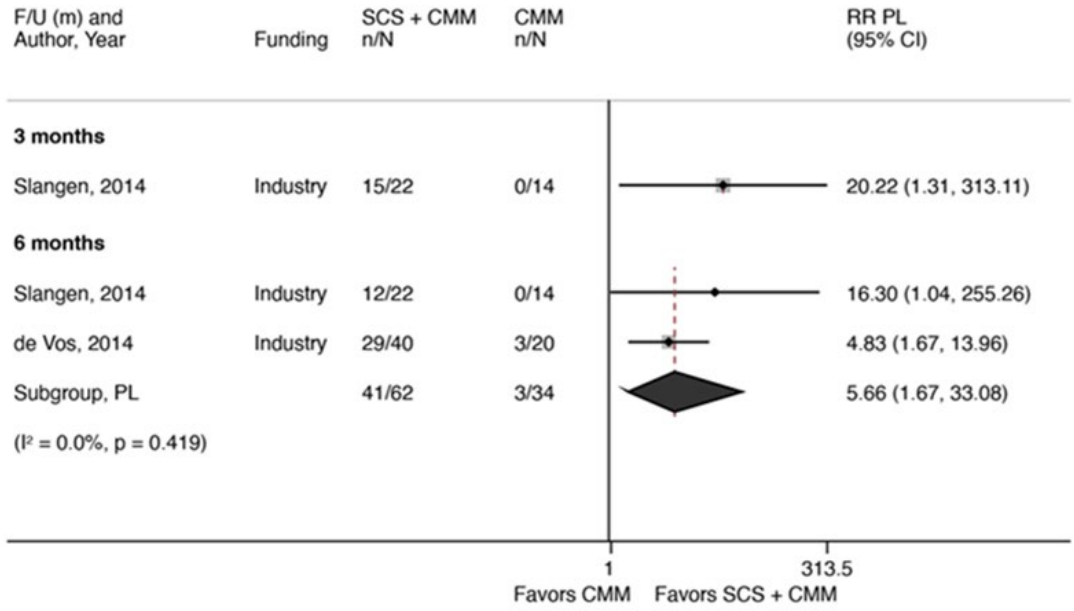
Patient satisfaction

HF (10 kHz)-SCS was associated with greater patient satisfaction compared with CMM alone at 6 months in one trial; 92% (80/87) of SCS versus 6% (6/93) of CMM patients (RR 14.25, 95% CI 6.56 to 30.98) reported being satisfied or very satisfied with their treatment.[127]

Patient global impression of change (PGIC)

The two trials of conventional SCS also reported pain "success" using the PGIC pain scale and defined responders as those with a score of 6 or higher. SCS (in addition to CMM) was associated with a large increase in the likelihood of achieving pain response on the PGIC compared with CMM alone at 3 months in one trial (N=36, 68.2% vs. 0%, RR 20.22, 95% CI 1.31 to 313.11)[147] and at 6 months across both trials (N=96, 66.1% vs. 8.8%, RR 5.66, 95% CI 1.67 to 33.08, I^2=0%)[33,147] (Figure 13), however, the maginitude of effect varied across the individual trials and the estimates were imprecise.

Figure 13. Patient global impression of change: SCS versus CMM for PDN



CI = Confidence interval; CMM = Conventional medical management; F/U = Follow-up; m = months; PDN = Painful Diabetic Neuropathy; PL = Profile likelihood; RR = Risk ratio; SCS = Spinal cord stimulation.

Composite measures

Two fair-quality trials[127,147] reported treatment success using composite outcomes and both found that SCS was associated with a substantial increase in the likelihood of treatment success compared with CMM alone. One trial compared HF (10 kHz)-SCS versus CMM and defined treatment success as a ≥50% improvement on VAS without observed deterioration on neurological examination at 3 months (ITT analysis, N=189, 78.9% vs. 5.3%, RR 14.84, 95% CI 6.29 to 35.05).[127] This was the authors' primary outcome and sensitivity analyses around varying assumptions for missing data did not change the conclusions. The second trial compared conventional SCS versus CMM and defined treatment success as ≥50% pain improvement on NRS for 4 days during daytime or nighttime or a score of ≥6 on a 7-point Likert scale of the PGIC scale for pain and sleep at 3 months (N=36, 72.7% vs. 0%, RR 21.52, 95% CI 1.39 to 332.40) and 6 months (N=36, 59.1% vs. 7.1%, RR 8.27, 95% CI 1.21 to 56.45); effect estimates were very imprecise.[147]

4.2.3 Complex Regional Pain Syndrome (CRPS)

4.2.3.1 SCS versus sham (placebo): Crossover RCTs

One multicenter, industry-funded, crossover RCT (N=33 randomized)[89] of SCS versus sham conducted in the Netherlands in patients with a confirmed diagnosis of CRPS was identified. The trial was registered on Current Controlled Trials database (registration number ISRCTN 36655259) and a published protocol was available[90]. Patients with a confirmed CRPS diagnosis in a single extremity with VAS pain score ≥5 (0-

10 scale) were eligible for inclusion. Patients were screened for psychological contraindications and patients were required to meet Dutch national guidelines for SCS implantation, however criteria were not detailed. Based on the number of patients analyzed (N=29), participants were predominantly male (68%) with a mean age of 43 years. Most patients had Type 1 CRPS (93%) that affected the lower extremity (62%). The median CRPS duration was 3 years (IQR 1-5 years). Comorbidities, cointerventions, and baseline medication use were not reported.

A two-week trial period with 40 Hz stimulation was conducted in 40 patients with 35 receiving permanent implants (87.5%) based on achieving >50% pain reduction and/or patient statement that symptoms were "much improved". All 35 patients had 12-weeks of tonic SCS (40Hz) pre-treatment phase prior to randomization to crossover period treatments; 33 patients were randomized. Four active SCS settings (standard 40 Hz SCS, 500 Hz SCS, 1200 Hz SCS, Burst SCS) were compared with a sham/placebo for 2 weeks per setting over a 10-week period with a 2-day washout period between settings. All patients randomly received all five settings. Of the 29 patients analyzed, 10% had prior SCS implantation. Following the crossover period, patients were able to choose their preferred settings for the following 3 months. This trial was considered fair quality. Study imitations include lack of clarity regarding care-giver blinding, the potential of 2-day washout period to inadequately mitigate any carryover effects (and no formal evaluation of this was done). As with other crossover trials in this review, although patients were considered blinded, the presence or lack of paresthesia for some treatments periods may have been noted by patients impacting blinding. No data following the first treatment phase were reported. While the primary outcomes described in the study protocol are reported, other listed outcomes (e.g., medication use) were not described in this publication.

4.2.3.1.1 Pain

This fair-quality trial reports VAS pain and McGill NRS average pain (0-10 scale for both). Direct comparisons adjusting for repeated measures/correlated data between different SCS modes (40 Hz SCS, 500 Hz SCS, 1200 Hz SCS, Burst SCS) and sham were not reported in this trial; the mean differences between individual frequencies and sham and confidence intervals were not reported.

Effect estimates and confidence intervals based on the authors' reported means that do not account for repeated measures analysis suggest that each of the SCS treatments was associated with moderate (1-2 points) to substantial (>2 point) improvement in VAS pain and on the McGill NRS average pain score, both on a 0-10 scale compared with sham/placebo stimulation (Table 16). A recent systematic review[121] that statistically adjusted for correlated data reported that while both the conventional (40 Hz) SCS and higher frequency (1200 Hz) SCS modes may be associated with improved VAS pain versus placebo, the results were similar between burst SCS and placebo. Substantial imprecision is noted in both the unadjusted and adjusted estimates; estimated values for this comparison in the confidence intervals range from those that are below the threshold for a small effect (for the unadjusted estimate) or small effect (adjusted) to a large effect (both estimates). Authors report that pain was similar across SCS modes during the washout period (with stimulation off), p=0.062.

4.2.3.1.2 Opioid use

Changes in opioid or other mediation use following treatment phases were not reported in this trial.

4.2.3.1.3 Secondary outcomes

Global Perceived Effect (GPE), improvement and satisfaction

The trial reported that all active SCS stimulations were associated with higher GPE satisfaction versus sham stimulation (p=0.001 across phases) and that improvement scores for the 40 Hz (standard) and 500 Hz were better versus placebo but that scores were similar between 1200 Hz or burst SCS versus placebo (Table 16).

Table 16. Summary of Outcomes Comparing SCS vs. Sham for Crossover Trial (Kriek 2016): CRPS

Outcome	SCS type	SCS Mean (SD)	Sham Mean (SD)	MD, (95% CI unadjusted)	MD, (95% CI adjusted) O'Connell – Cochrane
Primary Outcomes					
VAS Pain (0-10)	40 Hz	3.98 (2.53)	6.37 (1.89)	-2.39 (-3.57 to -1.22)	-2.39 (-4.35 to -0.43)
	500 Hz	4.01 (2.66)		-2.36 (-3.58 to -1.15)	Not calculated
	1200 Hz	4.29 (2.58)		-2.08 (-3.27 to -0.89)	-2.08 (-4.1 to -0.06)
	Burst	4.798 (2.82)		-1.58 (-2.84 to -0.31)	-1.5 (-3.79 to 0.65)
McGill NRS Average pain (0-10)	40 Hz	4.70 (2.15)	7.07 (1.51)	-2.37 (-3.35 to 1.39)	NR
	500 Hz	5.10 (2.42)		-1.97 (-3.03 to -0.91)	NR
	1200 Hz	5.31 (2.48)		-1.76 (-2.84 to -0.68)	NR
	Burst	5.66 (2.64)		-1.41 (-2.54 to -0.28)	NR
Secondary Outcomes					
Global Perceived Effect – Improvement	40 Hz	4.93(1.08)	3.79 (1.45)	1.14 (0.47 to 1.81)	NR
	500 Hz	5.0 (1.24)		1.21 (0.50 to 1.92)	NR
	1200 Hz	4.72 (1.13)		0.93 (0.25 to1.61)	NR
	Burst	4.55 (1.29)		0.76 (0.04 to 1.48)	NR
Global Perceived Effect – Satisfaction	40 Hz	5.28 (1.56)	3.52 (1.88)	1.76 (0.85 to 2.67)	NR
	500 Hz	5.31 (1.45)		1.79 (0.91 to 2.67)	NR
	1200 Hz	4.97 (1.40)		1.45 (0.58 to 2.32)	NR
	Burst	4.72 (1.83)		1.2 (0.22 to 2.17)	NR

CI = Confidence interval; CRPS = Complex regional pain syndrome; Hz = Hertz; MD = Mean difference; NR = not reported; NRS = Numerical rating scale; SCS = Spinal cord stimulation; SD = Standard deviation; VAS = Visual analogue scale.
* Authors do not report estimates of MD (95% CI) directly comparing different SCS modes with placebo but report p-values from modeling across SCS modes and sham. For all measures in this table, authors report that that each SCS modes were associated with improvement compared with sham.

4.2.3.2 SCS versus CMM or PT: Parallel RCTs

Two parallel RCTs evaluated SCS for the treatment of CRPS.[21,83]

One RCT (in three publications) (N=54, mean age 38 years, 68% female)[83-85] compared conventional SCS versus physical therapy (PT). CRPS duration was 3.3 years and was precipitated by trauma (48%) or surgery (44%) primarily and affected the hand (61%) or the foot (39%). All patients had failed CMM (for at least 6 months) prior to inclusion. Prior surgery, opioid use at baseline, and comorbidities were not reported. The SCS trial period was a minimum of 7 days and 67 percent of patients experienced a

successful trial leading to permanent SCS device implantation. It is unclear whether the trial period used the same SCS device. Appendix Table G10 provides details regarding SCS trial success criteria and SCS and PT treatment parameters. The follow-up period was 60 months. This trial was conducted in the Netherlands, received government funding, and reported no conflicts of interest. This trial was rated fair quality with the biggest limitation being the inability to blind providers and patients (who were also outcome assessors given the self-report nature of the outcomes). In addition, allocation concealment was not clearly described.

A second RCT (N=50)[21] compared HF (10 kHz) SCS (n=11) and conventional SCS (n=14) versus CMM (n=25). Patients' mean age was 49 years, 79 percent were female, and all but one patient (98%) were White. CRPS duration was an average of 3 years and was precipitated by trauma or surgery primarily and affected the upper extremity only. All patients had failed CMM prior to inclusion. Prior surgery, opioid use at baseline, and comorbidities were not reported. Given the small sample sizes in each group, several of the previously mentioned baseline characteristics were unbalanced between the three treatment groups (Appendix Table G10). Patients in the CMM arm were somewhat older and more commonly female. In both the HF SCS and CMM arms, CRPS was primarily due to trauma whereas in the LF SCS arm it was primarily due to surgery; the symptom duration was also longer in the HF SCS and CMM versus the LF SCS arm. Baseline VAS pain scores were higher in the two SCS arms versus the CMM arm (9.2 vs. 8.3). The SCS trial implantation period was 14 days and 86 and 91 percent of conventional and HF SCS patients, respectively, experienced a successful trial leading to permanent SCS device implantation. Appendix Table G10 provides details regarding SCS trial success criteria and SCS and CMM treatment parameters. It is unclear whether the trial period used the same SCS device. CMM consisted of pharmacological, physical, and blockage components; no other details were provided. Crossover was not allowed in this trial. The follow-up period was 12 months. This trial was conducted in Spain and reported no industry funding or conflicts of interest. The trial was rated poor quality due to unclear reporting of randomization and allocation concealment methods, inability to blind provider and patients (who were also outcome assessors given the self-report nature of the outcomes), differential loss to follow-up between treatment groups, and imbalances in important baseline characteristics at baseline (likely due to the small sample sizes in each arm). See Appendix E for details on study quality.

4.2.3.2.1 Pain

4.2.3.2.1.1 Pain Responders

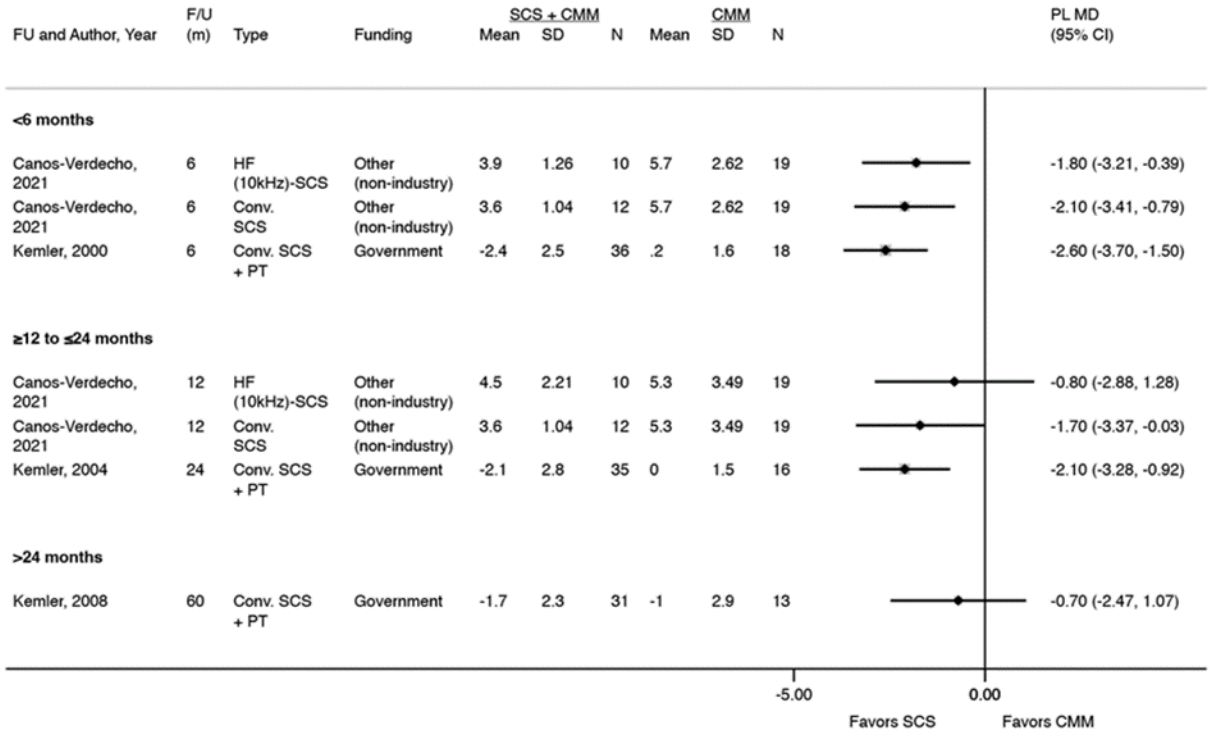
None of the included trials reported pain response.

4.2.3.2.1.2 Pain Scores

Two RCTs (one fair and one poor quality) reported pain scores on VAS or NRS (0-10 scale).[21,83] HF (10 kHz)-SCS was associated with a large improvement in pain at 3 months (N=29, MD -3.50, 95% CI -5.10 to -1.90) and a moderate improvement at 6 months (N=29, MD -1.80, 95% CI -3.21 to -0.39) compared with CMM, but results between groups at 12 months were similar (N=29, MD -0.80, 95% CI -2.88 to 1.28) in one poor-quality trial.[21] Across both trials, conventional SCS was associated with a large improvement in pain scores at 3 months (N=54, MD -2.60, 95% CI -3.70 to -1.50, 1 RCT[84]; N=31, MD -3.40, 95% CI -4.73 to -2.07, 1 RCT[21]) and at 6 months (2 RCTs, N=85, MD -2.39, 95% CI -3.39 to -1.34, I^2=0%)[21,83] and a moderate improvement at 12 to 24 months (2 RCTs, N=82, MD -1.97, 95% CI -3.08 to -0.77, I^2=0%)[21,84]

compared with CMM or PT but results between groups were similar at 60 months in one fair-quality trial (N=44, MD -0.70, 95% CI -2.47 to 1.07),[85] (Figure 14).

Figure 14. Pain scores (VAS or NRS, 0-10 scale): SCS versus CMM for CRPS



CI = Confidence interval; CMM = Conventional medical management; CRPS = Complex regional pain syndrome; F/U = Follow-up; HF = High frequency; kHz = Kilohertz; m = months; MD = Mean difference; NRS = Numerical rating scale; PL = Profile likelihood; PT = Physical therapy; SCS = Spinal cord stimulation; SD = Standard deviation; VAS = Visual analog scale.

One poor-quality trial reported the presence of neuropathic pain using Douleur Neuropathique 4 questions pain questionnaire (DN4).[21] Both types of SCS (conventional and HF (10 kHz) SCS) were associated with moderate improvements in pain at 3 months and small improvements at 6 months compared with CMM, but results between treatment groups were similar at 12 months (Table 17).

4.2.3.2.2 Function

Conventional SCS was associated with a moderate improvement in function on the ODI (0-100) at 3 months and a small improvement at 6 and 12 months compared with CMM in one poor-quality trial.[21] Conversely, HF (10 kHz) SCS was associated with less improvement at 6 months (small effect) and 12 months (moderate effect) compared with CMM in the same trial; results between groups were similar at 3 months (Table 17). The SCS groups had significantly worse ODI scores at baseline compared with the CMM group.

Table 17. Summary of other pain and function outcomes reported by CRPS trials

			Mean (SE)			MD (95% CI)	
Author, year	**Outcome**	**Timing**	**10 kHz SCS (n=10)**	**Conv. SCS (n=12)**	**CMM (n=19)**	**10 kHz SCS vs. CMM**	**Conv. SCS vs. CMM**
Canos-Verdecho, 2021 **ITT analyses**	DN4 (0-10, worst)	*Baseline*	*6.9 (0.4)*	*6.7 (0.3)*	*6.5 (0.3)*	*0.4 (-0.02, 0.82)*	*0.2 (-0.18, 0.58)*
		3 mos.	3.9 (0.3)	3.8 (0.6)	5.7 (0.4)	-1.8 (-2.14, -1.46)	-1.9 (-2.58, -1.22)
		6 mos.	3.8 (0.3)	3.9 (0.6)	4.9 (0.5)	-1.1 (-1.44, -0.76)	-1.0 (-1.72, -0.28)
		12 mos.	4.1 (0.4)	3.8 (0.6)	4.4 (0.7)	-0.30 (-0.73, 0.13)	-0.60 (-1.42, 0.21)
	ODI (0-100, worst)	*Baseline*	*65.0 (6.6)*	*58.5 (4.3)*	*32.4 (4.4)*	*32.6 (25.76, 39.44)*	*26.1 (20.56, 31.64)*
		3 mos.	29.4 (3.4)	17.3 (3.0)	31.5 (4.4)	-2.1 (-5.66, 1.46)	-14.2 (-18.81, -9.59)
		6 mos.	31.20 (3.6)	16.8 (3.0)	22.9 (4.5)	8.3 (4.54, 12.06)	-6.1 (-10.77, -1.43)
		12 mos.	33.2 (4.8)	17.0 (3.0)	22.0 (4.7)	11.2 (6.23, 16.17)	-5.0 (-9.79, -0.21)

CI = Confidence interval; CMM = Conventional medical management; CRPS = Complex regional pain syndrome; DN4 = Douleur Neuropathique en 4 Questions; ITT = Intention-to-treat; KhZ = Kilohertz; mos. = months; MD = Mean difference; ODI = Oswestry Disability Index; SCS = Spinal cord stimulation; SE = Standard error.

4.2.3.2.3 Secondary outcomes

Quality of Life and Depression

Conventional SCS and PT resulted in similar scores on the EQ-5D overall health VAS at 6, 24 and 60 months, the Nottingham Health Profile (NHP) scale at 24 and 60 months (authors state that SCS was associated with improvement in NHP pain component scores at 6 months but data was not reported), and the Self-Rating Depression Scale at 60 months in one fair-quality trial (Appendix Table F14).[83-85] In a second poor-quality trial, conventional SCS was associated with improvement in SF-12 Total, SF-12 physical, and SF-12 emotional scores at 3, 6 and 12 months compared with CMM, while HF (10 kHz) SCS was associated with improvement on all three measures at 3 months only (no difference at 6 and 12 months) compared with CMM.[21] The scale used for the SF-12 was unclear therefore effect sizes could not be assessed. See Appendix Table F15 for data.

Global Perceived Effect and Global Impression of Change

One fair-quality trial reported the proportion of patients with improvement in Global Perceived Effect (GPE), i.e., a score of 6 or 7 on the scale indicating much improved or best ever.[83-85] SCS (plus PT) was associated with a substantially higher likelihood of improvement in GPE compared with PT alone at 6 months (N=54, 38.9% vs. 5.6%, RR 7.00, 95% CI 1.00 to 49.12)[83] and 24 months (N=51, 42.9% vs. 6.3%, RR 6.86, 95% CI 0.99 to 47.52)[84] but results were similar between groups at 60 months (N=44, 22.6% vs. 15.4%, RR 1.47, 95% CI 0.35 to 6.14)[85]; however, effects estimates were very imprecise across all timepoints. All analyses were ITT. The second poor-quality trial reported both Patient- and Clinician-

rated Global Impression of Change scores with similar results between either type of SCS (conventional or HF (10 kHz) SCS) versus CMM at 3, 6 and 12 months (Appendix Table F15).[21]

4.3 Key Question 2: Safety of SCS

All four crossover RCTs[5,62,89,148] and all nine parallel RCTs (in 18 publications)[21,33,39,78,83-85,92,93,99,117,119,126-128,133,147,167] included for efficacy and three comparative NRSIs[37,125,164] included for effectiveness also reported safety outcomes. In addition, one retrospective comparative database study[97] and a total of 30 mostly retrospective single-arm studies – 21 case series (6 carried over from the previous report),[13,23,43,55,60,69,82,88,94,95,98,102,116,120,131,135,137,161,166,169,180] three registries,[20,34,130] and six database studies[6,47,52,61,73,96] – designed to evaluate the safety of SCS and met inclusion criteria were identified.

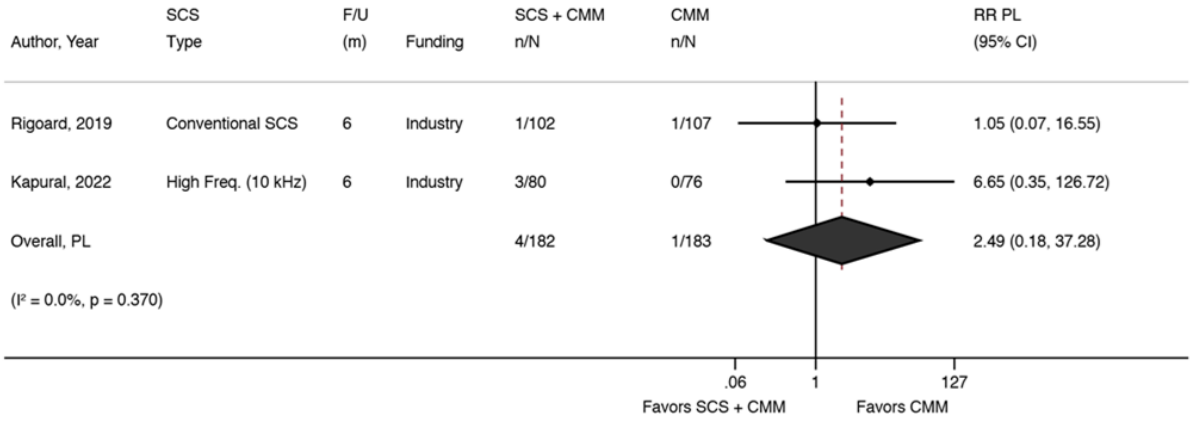
There was very little comparative safety data reported by the included trials. Most of the safety data presented was for the SCS arm of the trials only. We present safety outcomes in two sections: comparative safety and SCS-specific safety; the latter is further divided into any SCS-related event, device or hardware-related complications and biological complications with a focus on serious events and events requiring surgical intervention/reoperation. Ranges of frequencies are provided overall but information regarding the population (i.e., CLBP, PDN, CRPS) and device type used (conventional SCS or 10 kHz SCS) can be found in the tables (Table 20 and Appendix Tables F16- F18).

4.3.1 Comparative Safety

4.3.1.1 Withdrawals due to AEs

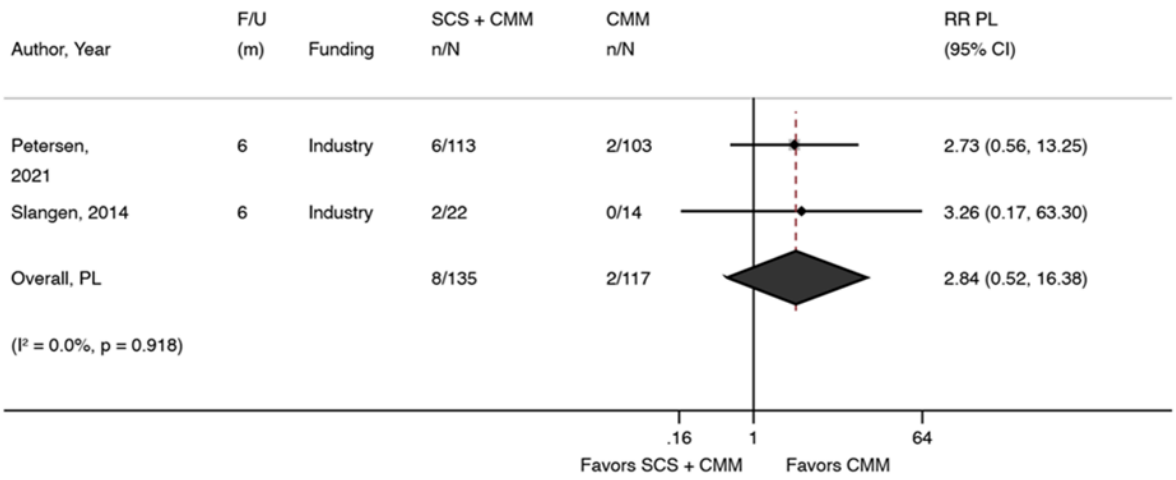
Four fair-quality parallel RCTs reported similar incidences of withdrawal due to AEs for SCS, both conventional and 10 kHz, versus CMM alone through 6 months, two in patients with FBSS or NSRBP (N=365, 2.2% vs. 0.5%; RR 2.49, 95% CI 0.18 to 37.28, I^2=0%)[78,133] and two in patients with PDN (5.9% vs. 1.7%; RR 2.84, 95% CI 0.52 to 16.38, I^2=0%)[127,147] (Figures 15 and 16).

Figure 15. Withdrawal due to AEs in trials of chronic back pain comparing SCS versus CMM



AEs = Adverse events; CI = Confidence interval; CMM = Conventional medical management; Freq. = frequency; F/U = Follow-up; kHz = Kilohertz; m = months; PL = Profile likelihood; RR = Risk ratio; SCS = Spinal cord stimulation.

Figure 16. Withdrawal due to AEs in trials of PDN comparing SCS versus CMM

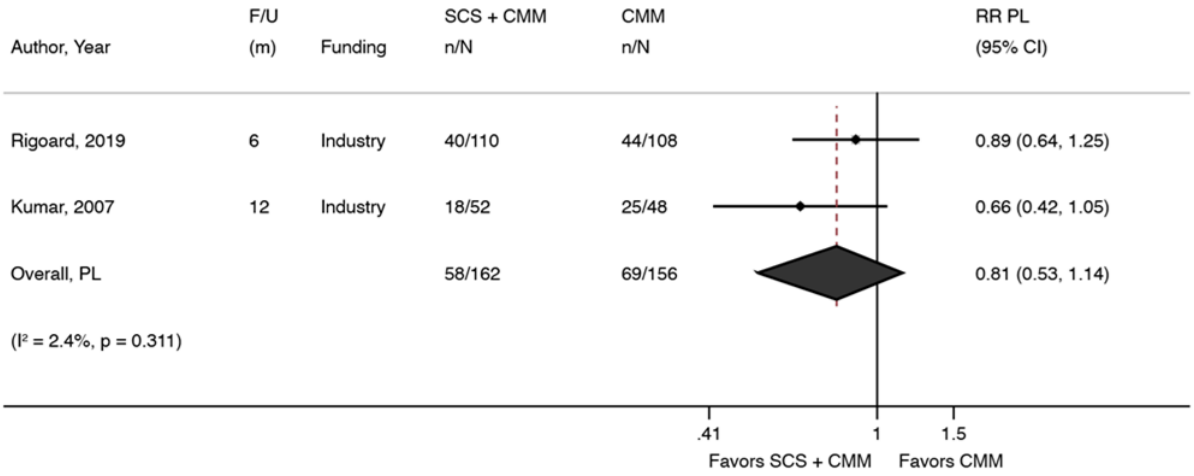


AEs = Adverse events; CI = Confidence interval; CMM = Conventional medical management; F/U = Follow-up; m = months; PDN = Painful diabetic neuropathy; PL = Profile likelihood; RR = Risk ratio; SCS = Spinal cord stimulation.

4.3.1.2 Any AE not related to SCS

Two fair-quality trials[92,133] in patients with FBSS reported the frequency of any non-SCS-related AEs which included a wide variety of complications (e.g., drug-related AEs; new illness or injury; worsening of pre-existing condition; other infection; thromboembolic or cerebrovascular events; cardiac, pulmonary, gastrointestinal or urinary events; headache, nausea, vomiting, or vertigo, etc.). The frequency of these events was similar between conventional SCS (in addition to CMM) versus CMM alone over 6 to 12 months follow-up (2 RCTs, N=318, 35.8% vs. 44.2%, RR 0.81, 95% CI 0.53 to 1.14, I^2=2.4%), Figure 17.

Figure 17. Any AE not related to SCS in trials of FBSS comparing SCS versus CMM



AE = Adverse event; CI = Confidence interval; CMM = Conventional medical management; FBSS = Failed back surgery syndrome; F/U = Follow-up; m = months; PL = Profile likelihood; RR = Risk ratio; SCS = Spinal cord stimulation.

One fair-quality retrospective database study (MarketScan insurance claims data set) (N=16,455) evaluated the frequency of peri- (index visit) and post-operative (1 and 3 months) complications following SCS implantation versus lumbar reoperation for the treatment of FBSS.[97] Although the trial did conduct a propensity score matched analysis for health care resource use outcomes, it did not do so for adverse events. Mortality at the index visit was low with similar frequencies between the two groups (SCS, 0% [0/395] vs. reoperation, 0.12% [20/16,060]). SCS was associated with a significant reduction in the risk of any complication (i.e., renal, cardiac, neurological, DVT/PE, pulmonary, infection, and wound) compared with reoperation at all timepoints: index visit (5.1% vs. 11.7%), 1 month (6.7% vs. 14.4%) and 3 months (6.5% [22/338] vs. 14.4% [2074/14,386]; RR 0.45, 95% CI 0.30 to 0.68; RD -7.9%, 95% CI -10.6% to -5.2%). This finding was driven primarily by the lower frequency of wound complications in the SCS group: index visit (1.3% vs. 5.8%), 1 month (2.0% vs. 7.3%) and 3 months (2.8% [11/338] vs. 7.6% [1221/14,386]; RR 0.38, 95% CI 0.21 to 0.69; RD -5.2%, 95% CI -7.2% to -3.3%). Pulmonary complications also tended to be lower in the SCS vs. the reoperation group, but the differences did not reach statistical significance. There were no other differences between the treatment groups in individual complications, to include infection rates.

4.3.2 SCS-specific Safety

The adverse events reported in the section pertain specifically to the SCS devices or procedures; thus all sample sizes (n's) reported reflect the number of patients in the SCS arms of the studies. For the RCTs, events prior to 6 months reflect either all patients who underwent trial stimulation or those who received a permanent implant, depending on what the authors reported. Timepoints after 6 months (after crossover) may include all patients who received permanent implant regardless of initial randomization (i.e., includes those who crossover to SCS after 6 months), again depending on what was reported by the authors. There is overlap in events between some of the individual adverse events categories below, e.g., if a serious infection led to device explanation that patient was counted under device explantation and serious infection.

4.3.2.1 Crossover RCTs

4.3.2.1.1 FBSS or Chronic Radiculopathy

Two trials[62,148] described SCS-related adverse events. Small sample sizes in both trials likely precluded detection of uncommon events (Table 18). The larger, higher quality trial, 18% (9/50) of patients had an adverse event, noting that no patient experienced more than one event[62]. Across the two trials, IPG removal occurred in 5.9% (4/68); removal in one trial[62] (one patient) was attributed to deep infection and the other trial[148] indicated removal was unavoidable but did not specify reasons for removal. The same small trial reports a 13% (n=NR) of patients had removal of electrodes and IPGs due to unsatisfactory pain relief. It is unclear whether patients could experience more than one event in this trial. IPG replacement occurred in 2% of patients across the 2 trials, and lead/electrode revision or replacement was more common (7.4%, 5/68). Allergic reactions, including anaphylaxis, may be uncommon and studies may have been underpowered to detect this. Unintentional durotomy was reported in 6% (3/50) of patients in one trial[62].

In the third trial[5], two individuals withdrew due to adverse events. One occurred during screening (1/53); it is unclear if this was prior to device implantation. The other withdrawal during the device testing trial (1/39). Event types and possible relationship to SCS were not described. Authors claim that no adverse neurological sequelae occurred from use of high frequencies.

All trials were likely underpowered to detect rare or uncommon events.

Table 18. Summary of Adverse Events Reported in Crossover Trials in Patients with FBSS or Chronic Radiculopathy Following Lumbar Spine Surgery

Adverse event	Timing	Study (year), % (n/N)	Estimate across studies
IPG removal			
Unavoidable IPG removal (NOS)	NR	Sokal (2020), 16.7% (3/18)	5.9% (4/68)
Deep infection requiring removal	Within 12 weeks	Hara* (2022), 2% (1/50)	
IPG, electrode removal due to unsatisfactory pain relief	NR	Sokal (2020), 13% (NR)	NA
IPG replacement			
Pulse generator replacement	Within 12 weeks	Hara* (2022), 2% (1/50)	2.9% (2/68)
IPG replacement; depleted battery	10 months	Sokal (2020), 5.6% (1/18)	
Lead revision or replacement			
Lead revision	Within 12 weeks	Hara* (2022), 8% (4/50)	7.4% (5/68)
Electrode replacement (dysfunction)	NR	Sokal (2020), 5.6% (1/18)	
Allergic reaction			
Delayed allergic reaction	13 months	Sokal (2020), 5.6% (1/18)	NA
Anaphylactic reaction	Within 12 weeks	Hara* (2022), 0% (N=50)	NA
Other reported AEs			
Any AE	Within 12 weeks	Hara* (2022), 18% (9/50)	NA
Unintentional Durotomy	Within 12 weeks	Hara* (2022), 6% (3/50)	NA
Superficial infection (antibiotics)	Within 12 weeks	Hara* (2022), 2% (1/50)	NA
Micturition problems	Within 12 weeks	Hara* (2022), 2% (1/50)	NA
Withdrawal due to AE (NOS)	Screening Device trial	Al-Kaisy (2018), 1.9% (1/53) Al-Kaisy (2018), 2.6% (1/39)	NA
Post-op hematoma, pneumonia, thromboembolism, cardiovascular complication, urinary tract infection	Within 12 weeks	Hara* (2022), 0% (N=50)	NA

AE = adverse event; IPG = implantable pulse generator; FBSS = failed back surgery syndrome; NA = not applicable; NOS = not otherwise specified; NR = not reported.

* No patient experienced more than 1 event.

4.3.2.1.2 CRPS

The one crossover trial[89] comparing SCS modes (40 Hz SCS, 500 Hz SCS, 1200 Hz SCS, Burst SCS) versus sham stated that no serious adverse events occurred. Other adverse events during the crossover periods are summarized below (Table 19). Authors do not report on AEs during the open phase where patients had a choice of frequency.

Table 19. Summary of Adverse Events During the Crossover Period; Kriek 2016

Adverse event during crossover	% (n/N) patients or number events
Device related	
Long/frequent charging times	22 events (11 during 1200 Hz)
Electrode dislocation	10% (3/29)
Stimulation switches off	3.4% (n=1/29, during 1200 Hz)
Programming related	
Electrode reconfiguration	8 events
Adjusted pulse width	27 events (20 events during 1200 Hz)
Comfortable paresthesia not reached	24% (n=7/29; n=1 with standard, n=6 with 1200Hz)
Pmax too high	8 events (5 during 1200 Hz)
Stimulation related	
Headache	4 events
Itching or rash	6.9% (2/29)
Unable to set stimulation high enough	3 events (2 during 1200 Hz)
Trial SCS set at 60Hz (vs. 40 Hz) for standard SCS	3.4% (1/29)
Patient related	
Stimulation discontinued (NOS)	1 event; switched off until next stimulation period
Patient converted to standard stimulation (NOS)	3 events

Hz = Hertz; NOS= not otherwise specified.

4.3.2.2 Parallel RCTs

4.3.2.2.1 Mortality

Only two small RCTs reported mortality related to or possibly related to the device/study, for a total of two events (5.1%, 2/39), Table 20. In one trial,[147] a 65-year-old male (5.3%, 1/19) with PDN suffered a dural puncture (and subsequent postdural puncture headache) during lead implantation for the SCS test stimulation; three days after discharge, his headache worsened and he became unresponsive. A large subdural hematoma in the left hemisphere had caused a midline line shift of 19.8 mm and despite immediate treatment he died 10 days later. In the other trial, one patient (5%, 1/20) randomized to SCS for the treatment of FBSS suffered a cardiac event near the 6 month follow-up; no further information was provided.[119]

4.3.2.2.2 Any SCS-related AE

Across four RCTs, two in patients with FBSS,[92,133] one in patients with NSRBP[78] and one in patients with PDN[127], the frequency of any SCS-related AE ranged from 12.4% to 17.6% at 6 months (2 RCTs, N range 102 to 113)[127,133] and from 24.1% to 32.1% at longest follow-up, 12 to 24 months (3 RCTs, N range 84 to 174),[78,92,133] Table 20. Events included device or hardware issues, loss of therapeutic effect or paresthesia issues, technique issues and biological complications. Many patients had more than one event.

4.3.2.2.3 Any SCS-related AE requiring surgery

Across three RCT, two in patients with FBSS[92,133] and one in patients with CRPS,[83-85] the frequency of any SCS-related AE (as described above) requiring surgery to resolve ranged from 11.8% to 16.7% at 6 months (2 RCTs, N range 24 to 102),[83,133] from 23.8% to 37.5% at 12 to 24 months (2 RCTs, N range 24 to

84),[84,92] and was 41.7% in one small RCT (n=24)[85] at 60 months (Table 20). Many patients had more than one event.

4.3.2.2.4 Any Serious SCS-related AE

Four RCTs reported the frequency of any SCS-related AE described as serious by the authors (Table 20). At 6 months, two RCTs (in patients with PDN) reported serious AEs in two patients each (1.8% [2/113][127] and 10.5% [2/19][147]); by 24 months, seven patients (4.5%) had suffered a serious AE in one of these trials.[128] The larger trial[127,128] did not report what the serious AEs were and in the smaller trial[147] there was a dural puncture during the trial stimulation that lead to death (also reported above under mortality above) and an infection leading to explant. A third trial in patients with NSRBP reported that six patients suffered a serious event by 12 months (4.1%, 6/145) which included two implant site infections (requiring IPG explant and reimplantation), and one sensory deficit (attributed to 10-kHz SCS stimulation, resolved after adjustment), poor wound healing (treated with device explant), lethargy (due to narcotic use) and osteomyelitis (as a complication of the trial, did not receive a permanent implant) in one patient each (0.7%, 1/145).[78] The fourth trial, in patients with FBSS, reported that 13 serious events occurred at 6 months (n=102), over half of which were implant site infections (7 events), and 24 serious events by 24 months (n=174), but did not provide the number of patients affected.[133]

Table 20. Summary of Adverse Events

Outcome	Author, year	Population	SCS	Follow-up	%, n/N	No. events
Mortality	Slangen, 2014	PDN	Conv.	6 mos.	5.3% (1/19)	n/a
	North, 2005	FBSS	Conv.	mean 3 years	5.0% (1/20)	n/a
Any SCS-related AE	Rigoard, 2019	FBSS	Conv.	6 mos.	17.6% (18/102)*	21
				24 mos.	25.3% (44/174)†	63
	Kumar, 2007	FBSS	Conv.	12 mos.	32.1% (27/84)‡	40
	Kapural, 2022	NSRBP	10 kHz	12 mos.	24.1% (35/145)†	41
	Petersen, 2021	PDN	10 kHz	6 mos.	12.4% (14/113)§	18
Any SCS-related AE: Surgery required	Rigoard, 2019	FBSS	Conv.	6 mos.	11.8% (12/102)	NR
	Kumar, 2007	FBSS	Conv.	12 mos.	23.8% (20/84)	NR
	Kemler, 2000	CRPS	Conv.	6 mos.	16.7% (4/24)	NR
	Kemler, 2004			24 mos.	37.5% (9/24)	22
	Kemler, 2008			60 mos.	41.7% (10/24)	29
Any SCS-related AE: Serious	Rigoard, 2019	FBSS	Conv.	6 mos.	NR	13
				24 mos.	NR	24
	Kapural, 2022	NSRBP	10 kHz	12 mos.	4.1% (6/145)	6
	Petersen, 2021	PDN	10 kHz	6 mos.	1.8% (2/113)	2
	Petersen, 2023	PDN	10 kHz	24 mos.	4.5% (7/154)†	NR
	Slangen, 2014	PDN	Conv.	6 mos.	10.5% (2/19)	2

AE = Adverse event; CRPS = Complex regional pain syndrome; FBSS = Failed back surgery syndrome; kHz = Kilohertz; mos. = months; no. = number; NSRBP = nonsurgical refractory back pain; PDN = Painful diabetic neuropathy; SCS = Spinal cord stimulation.

* Out of all patients who underwent a trial stimulation.
† Out of all patients patient who underwent trial stimulation (both in original SCS arm and crossover arm)
‡ Out of all patients who underwent trial stimulation or received a permanent implant (both in original SCS arm and crossover arm)
§ Out of all randomized patients

4.3.2.2.5 Device or hardware specific AEs

All nine RCTs reported device or hardware related AEs (Appendix Table F16).

One trial in FBSS patients reported that 13.1% (11/84) of SCS patients experienced a total of 13 **hardware-related AE event** by 12 months; in all but one patient (11.9%, 10/84) surgical revision was required.[92]

Explantation was reported by five trials (in 9 publications) (1 FBSS, 1 NSRBP, 2 PDN, 1 CRPS; N range 19 to 154) and occurred in 1.4% to 5.3% of patients over 6 months to a mean of 3 years follow-up.[78,83-85,119,126-128,147] The primary reason for device explant in these trials was infection. The trial in patients with CRPS also reported a total of three system explantations after 6 months through 60 months (all occurred by 24 months) but it is unclear if this represents patients or events.[84,85] Additionally, two of these trials (both HF 10 kHz SCS) reported that no device was explanted due to loss of therapeutic effect/efficacy over 12 to 24 months.[78,126,128]

Adverse events that we classified as **device failure or malfunction** were reported by six RCTs (2 FBSS, 2 PDN, 2 CRPS; N range, 12 to 174)) with frequencies ranging from 1.1% to 41.7% over 6 to 24 months follow-up.[21,33,84,92,127,133] Excluding the very small, outlier trial (n=12)[21] that reported annoying paresthesia with postural changes in five patients through 12 months, the range was 1.1% to 7.1%. Considering only those events that required surgery/revision, the range was 1.2% to 5.6%. Most of the events were related to paresthesia such as painful paresthesia or other uncomfortable sensations (5 RCTs),[21,84,92,127,133] loss of paresthesia or therapeutic effect (2 RCTs)[92,133] and incomplete overlap of paresthesia with painful area requiring a second electrode lead (1 RCT)[33]. In addition, one trial reported device deployment issues and device stimulation issues (not otherwise specified) over 24 months; the only events considered serious as reported by any trial were these device stimulation issues (2.0%, 2/102) which occurred by 6 months and required surgery to resolve.[133]

The frequency of **IPG revision or replacement** ranged from 0.9% to 8.3% across five trials (in 9 publications) (2 FBSS, 1 NSRBP, 1 PDN, 1 CRPS; N range 24 to 174) with 6 to 24 months follow-up.[78,83-85,92,126-128,133] One small trial reported that two patients experienced serious pulse generator pocket pain requiring revision by 6 months (8.3%, 2/24)[83]; excluding this trial the frequency ranged from 0.9% to 3.2% (N range, 84 to 174). No other trial described events as serious. Reasons for revision or replacement included device dislocation, IPG migration or extrusion, and repositioning due to implant site pain. Additionally, one of these trials reported that 54.2% of patients (13/24; 17 total events) had a IPG replacement over a 60 month follow-up period but did not indicate the cause; there were also eight pulse generator pocket revisions through 60 months in this trial but it is unclear if this number represent patients or total events.[84,85]

Lead/electrode failure or migration was reported by six RCTs (in 10 publications) (2 FBSS, 1 NSRBP, 2 PDN, 1 CRPS; N range 24 to 145).[33,78,83-85,92,119,126-128] The frequency of lead migration or lead

fracture/torqued contacts without mention of revision ranged from 1.0% to 9.5% across three trials (N range 36 to 113) over 6 to 12 months follow-up[33,92,127]; the frequency of complications resulting in revision, replacement or repositioning ranged from 0.6% to 20.8% across five trials (in 6 publications) (N range 24 to 154)[78,83,92,119,126,128] over 6 months to a mean of 2.9 years and included lead migration, malposition, dislodgement, and fracture, defective leads, and lack of therapeutic effect. The exclusion of one small trial (n=24)[83] that reported revision due to unsatisfactory positioning of the electrodes through 6 months, the frequency of lead complications requiring surgical interventions ranged from 0.6% to 10% . This same small trial (n=24)[84,85] reported 11 lead repositionings and six lead replacements through 60 months but it is unclear if these numbers represent patients or total events.

One trial in patients with FBSS reported one issue related to the **device battery** through 24 months that did not require surgery (0.6%, 1/174).[133]

4.3.2.2.6 Biological or Surgical Complications

Eight RCTs (in 12 publications) reported biological or surgical complications.[21,33,78,83-85,92,126-128,133,147]

Two trials (1 FBSS and 1 CRPS) reported the frequency of **any biological event** which ranged from 19% to 25%. The FBSS trial reported serious complications in six (of the 16) patients (7.1%, 6/84) through 12 months.[92] The CRPS trial reported a total of 11 events in six patients (25%, 6/24) by 6 months but did not indicate whether any were serious.[83]

Infection rates were reported by seven RCTs (in 9 publications) (2 FBSS, 1 NSRBP, 3 PDN, 1 CRPS; N range, 24 to 174) over 6 to 24 months follow-up which ranged from 2.7% to 8.3%.[33,78,83,92,126-128,133,147] The rate of serious infection was 1.4% to 6.0% across five of the trials (N range, 19 to 174)[78,83,92,133,147] and the rate of serious infections requiring surgery was 4.2% to 6.0% across three trials (N range, 24 to 102).[83,92,133] One trial also reported that one patient had cellulitis (0.6%, 1/174) over 24 months of follow-up but did not reported the severity.[133]

A variety of **possible surgical or technical complications** were reported by five RCTs (2 FBSS, 1 NSRBP and 1 CRPS; N range 10 to 174).[21,78,83,92,133] In two of these RCTs, all events were considered serious and included one case of extradural hematoma and one postprocedural complication (no other details provided) (0.6% for both; 1/174) over 24 months in one trial[133] and five cases of SCS-related technical complications (not further described) in four patients (4.8%; 4/84) by 12 months in the other trial.[92] One of these trials also reported four patients with neurostimulator pocket fluid collection (4.8%, 4/84) but these were not described as serious.[92] Across the other three trials, there were three patients with transient CSF leakage (2.0%; 3/145),[78] two patients with dural puncture (8.3%; 2/24),[83] one patient with occipital headache (10%; 1/10)[21] in one trial each across 6 to 24 months. None of the latter events were described as serious by the authors.

Implant or incision site pain (or swelling) was reported by seven RCTs (2 FBSS, 1 NSRBP, 2 PDN and 2 CRPS). Across the six RCTs that provided data using the number of patients, the frequency of this complication ranged from 0.6% to 10% (N range, 10 to 174)[21,33,78,92,127,133]; excluding the very small trial (n=10)[21] the range was 0.6% to 6.0%. A total of two events were considered serious by the authors: two FBSS trials reported one patient each (1.0%) with implant/incision site pain that required surgical intervention.[92,133]

Neurological injury was reported by four trials (in 5 publications), one of which (10 kHz SCS in PDN patients, N=134)[127,128] indicated that no stimulation related neurological deficits occurred over 24 months. Across the other three trials there were two serious events, neurological/sensory deficit in one trial through 12 months (0.7%, 1/145)[78] and autonomic neuropathy in another trial by 6 months(5.3%, 1/19)[147]; the third trial[133] reported one patient (0.6%, 1/174) with non-serious monoparesis through 24 months follow-up.

Skin-related complications included contact dermatitis in two patients across two trials (0.6%-0.9%)[127,133] and urticaria in one patient in one trial (0.9%)[127]; none were serious.

A wide variety of **other** adverse events were reported across five trials. Two trials reported ***serious events*** which occurred in one patient each and included back pain, lower abdominal pain, musculoskeletal pain, pulmonary edema and UTI in one trial in FBSS (0.6% ; 1/174, through 24 months)[133] and severe lethargy due to narcotic use, osteomyelitis and poor wound healing in the other trial in NSRBP (0.7%; 1/145, through 12 months).[78] The frequency of various other nonserious events ranged from 0.6% to 2.8% across three trials[33,127,133]; one trial reported a total of seven events through 24 months.[84]

4.3.2.3 Nonrandomized Comparative Studies of Interventions (NRSIs)

4.3.2.3.1 Device or hardware specific AEs

Device explanation or removal rates across the NSRIs were higher than those reported by the RCTs One prospective NRSI in patients with FBSS and 24 months of follow-up reported a **device explantation** rate of 22.2% (6/27) in patients who underwent permanent implantation; the authors also report a device explantation and replacement in one patient (3.7%) but it is unclear if this patients is different from those already counted under device explantation only. In addition, **revision of the IPG or lead** was reported in 11.1% (3/27) and 14.8% (4/27) of patients, respectively. [164] Similarly one retrospective propensity-scores matched database evaluating SCS for the treatment of (primarily, 71%) FBSS[37] reported any **removal or revision of the IPG generator or lead** in 22.1% (279/1260) of patients who had permanently implanted devices through 24 months - in 10% (126/1260) of these cases removal/revision was in the absence of a complication suggesting lack of effectiveness. **Any lead/generator-related AE** (e.g., breakdown, displacement, infection/inflammation, other mechanical complications) was reported in 17.9% (226/1260) of patients. The second prospective NRSI (n=39 in SCS group) did not report safety data and only mentioned that three patients (7.7%) in the SCS arm needed minor reoperations, but no further information was provided.[125]

4.3.2.3.2 Biological or Surgical Complications

Only one prospective NRSI in patients with FBSS and 24 months of follow-up reported biological or other potentially serious adverse events. [164] Among patients who had permanently implanted devices (n=28), implantation was terminated due to dural puncture and CSF leak in one patient (4%) and five patients (18%) experienced persistent pain over SCS components but it is not clear whether this lead to revision in any patient. Superficial infections were reported in three patients (11%). When all patients who underwent at least trial stimulation were considered (n=51), eight patients (16%) had an adverse event associated with trial stimulation which included three serious or potentially serious events in one

patient (2%) each: severe post-spinal headache, fluid leaking at electrode entry site, extensive epidural abscess that necessitated irrigation, debridement, and a T2-L3 hemilaminotomy; one day following surgery, the patient had respiratory arrest and was placed on mechanical ventilation. The other five patients (10%) complained of symptoms of unknown etiology such as dizziness and increased back or leg pain. In addition, one patient in the SCS group died (2.0%, 1/51) between the 6 and 12 months follow-ups but the cause was not reported.

4.3.2.4 Case series, database studies and registries

Adverse events were variably classified, described, and reported across included nonrandomized case series and administrative database studies. These types of studies may suffer from selection bias. Administrative database and registry studies may not adequately control potential confounding factors that may impact frequency of adverse events.

Five case series with at least five years follow-up were included in the prior report[82,94,95,120,137] and are included here. In addition, 16 additional case series[13,23,43,55,60,69,88,98,102,116,131,135,161,166,169,180] designed specifically to evaluate AEs with either a minimum of five years follow-up and/or described uncommon or rare events (e.g., infection) were included as were nine large registry and administrative databased studies.[6,20,34,47,52,61,73,96,130]

The following results focus on serious events to the extent possible. We also focus on studies with longer length of follow-up larger and sufficient sample size to identify rare events. Detailed data abstraction of adverse events is found in Appendix F, full data abstraction tables. Summary tables listed the studies included for the adverse events listed below can be found in Appendix Tables F18 to F23.

Explanation: Multiple reasons for explanation were described across nonrandomized studies. Studies were not always clear if the IPG and/or electrodes were being explanted. Some studies that reported overall or total explant rates frequently provided reasons for explant and it was not always clear whether patients may have experienced more than one reason. Any or total number of explant frequency ranged from four percent to 27.7 percent in studies with over 500 patients, frequency due to infection ranged from 0.3 percent to 4.9 percent, frequency due to inadequate pain relief, lack of efficacy, inadequate benefit or loss of efficacy ranged from one percent to 25.9 percent, frequency due to pain or discomfort at the IPG site or electrodes or otherwise intolerable pain ranged from 0.4 percent to 9.3 percent, and explant frequency due to device malfunction, electrode migration or dysfunction, or "no longer joinable" ranged from 0.3 percent to 13.0 percent.

IPG revision or replacement: Multiple reasons for IPG revision or replacement were described across nonrandomized studies. Studies were not always clear regarding whether an event resulted in revision or replacement or whether patients experienced multiple events reported separately leading to revision or replacement. Any or total number of IPG revision or replacement frequency ranged from 3.1 percent to 63.0 percent in included studies, frequency due to infection was 2.7 percent with only one study reporting this, frequency due to pain or discomfort at the IPG site or in the IPG pocket ranged from 0.9 percent to 31.6 percent, frequency due to IPG or electrode malfunction or intolerable pain ranged from 1.4 percent to 7.4 percent, frequency due to IPG displacement or migration ranged from 0.5 percent to 1.4 percent, and frequency of IPG revision or replacement due to battery failure, electrical leak, or charging problems ranged from 0.5 percent to 78.9 percent.

Lead or electrode events: Multiple lead or electrode events were described across nonrandomized studies. Studies were not always clear regarding whether patients experienced multiple events reported separately leading to the same event. Any or total number of lead or electrode event frequency ranged from 3.4 percent to 22.5 percent in included studies, frequency of lead fracture or failure ranged from 1.1 percent to 42.1 percent, frequency due to pain or discomfort at the IPG site or in the IPG pocket ranged from 0.9 percent to 31.6 percent, frequency due to IPG or electrode malfunction or intolerable pain ranged from 1.4 percent to 7.4 percent, frequency lead migration or mispositioning ranged from 1.1 percent to 33.5 percent, and frequency of inadequate or inappropriate paresthesia or pain or high impedance due to lead or electrode event ranged from 5.4 percent to 26.4 percent.

Infection events: Multiple infection events were described across nonrandomized studies. Studies were not always clear regarding severity of infection or whether the infection resulted in additional procedures or hospitalization. Frequency of deep, serious, or fatal infection or infection leading to hospital readmission or device revision or replacement ranged from 0.4 percent to 8.0 percent in included studies, frequency of superficial, not fatal, or non-serious infection without readmission or device revision or replacement ranged from 0.5 percent to 9.3 percent, and frequency of infection of unspecified intensity or outcome ranged from 0.6 percent to 4.3 percent.

Miscellaneous biological events: Multiple biological events were described across nonrandomized studies. Studies were not always clear regarding cause of event or whether an individual experienced multiple events. Frequency of cerebrospinal fluid (CSF) leak or dural tear ranged from 0.6 percent to 7.1 percent in included studies, frequency of neurological deficit, paralysis, or intraspinal abscess ranged from 0.2 percent to 0.9 percent, frequency of cardiac complication or pulmonary embolism ranged from 0.3 percent to 0.5 percent, frequency of allergic reaction ranged from 0.2 percent to 0.7 percent, and frequency of hematoma, seroma, or hemorrhage ranged from 0.1 percent to 5.7 percent.

Miscellaneous events leading to hospitalization or a trip to the emergency department: Multiple miscellaneous events resulting in hospitalization or a trip to the emergency department but not includable in other classifications of adverse events or not specifying reason for hospitalization were described across nonrandomized studies. Frequency of miscellaneous events leading to hospitalization or a trip to the emergency department ranged from 0.7 percent to 20.9 percent.

4.4 Key Question 3: Differential Efficacy and Safety of SCS

None of the trials identified that met inclusion criteria reported subgroup analyses or did formal tests for interaction to evaluate heterogeneity of treatment effect for spinal cord stimulation.

4.5 Key Question 4: Cost-effectiveness of SCS

Summary of studies and key points:

Three[118,143,155] full economic studies were included in the prior, 2010 HTA, one[143] of which was part of a 2009 NICE HTA; only one[118] was conducted in the U.S. The prior report concluded that evidence from these studies suggest 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 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.

Eight full economic studies[9,36,70,86,91,124,134,146] published subsequent to the prior report met the inclusion criteria. Six studies were of fair or good quality (QHES ranges 81/100 to 94/100), with two rated as poor quality (QHES 60/100, 73/100). Six studies evaluated SCS cost-effectiveness for FBSS or back pain [9,36,70,91,124,134]. Two of these also evaluated cost-effectiveness for CPRS[36,91] as did another study[86]. Only one study was in patients with PDN[146]. Two studies[70,124] were United States based, two were conducted in the United Kingdom[9,86], and one each in Canada[91], Spain[134], Australia[36] and the Netherlands [146]. Funding was not reported in one study[9], one was funded by government-related non-profit organization[91], and one was prepared for a professional organization[36]. The other five were industry sponsored.

Data for clinical outcomes across the economic analyses were generally from small clinical studies; studies may have been underpowered to identify and model important rare events. Studies cite the lack of high-quality comparative data, particularly for newer SCS modes (e.g., HF-SCS) and for long term outcomes. Many modeled time horizons that extended beyond available clinical data. The back pain studies cite and rely on similar modeling methods, assumptions and data used in older studies. While many studies followed accepted methods for full economic analysis based on the QHES, assumptions about and modeling of effectiveness and harms, particularly longer term were not well articulated or supported clinical data from methodologically rigorous clinical studies in most studies. The range of effectiveness and frequency of harms were not generally evaluated in sensitivity analyses thus the impact of these as drivers of cost-effectiveness is not clear. Findings across the more recent studies are generally in line with the findings of the 2010 report.

Key Findings across new studies:

- **FBSS and back pain**
    - Two U.S. based studies, one in patients with FBSS and another in patients with nonsurgical refractory back pain (NSRBP) were included.
        - One good quality cost-effectiveness study[70] in a Worker's Compensation population with FBSS found that that SCS is not cost effective at commonly considered WRT thresholds of either $50,000 or $100,000 compared with usual care or referral to a dedicated pain clinic over a 24-month time horizon. The applicability of these findings to other populations is unclear. Authors also note that fewer patients had a successful SCS trial (53%) in the prospective cohort compared with what may be reported in RCTs in other populations.
        - One poor quality CUA[124] in patients with NSRBP reported a base-case ICER for 10-kHz SCS therapy combined with CMM of -$2,236/QALY at 6 months, significantly below the willingness-to-pay threshold of $50,000/QALY compared with CMM alone. Modeling of adverse events was not well described. When a mean cost of $30,000 for reimbursement for initial SCS and procedure costs was modeled, an ICER of over $200,000 at 6 months and approximately $100,000 QALY at 12 months (estimated from author's figure) is suggested. Authors state that cost-effectiveness can be achieved within 2.1 years when these costs are included.

  - Four CUAs conducted outside of the U.S[9,36,91,134]. evaluated the cost effectiveness of SCS plus CMM with CMM alone in patients with FBSS. Three were of good quality, one was poor quality.
    - All concluded that SCS + CMM was more cost-effective than CMM alone based on usual willingness to pay thresholds.
    - One study also compared SCS with reoperation, reporting that SCS was more cost-effective.
    - Primary limitations of these studies include modeling of time-horizons that extend beyond available clinical data and unclear modeling of long-term benefits and complications. Not all included initial SCS trial or implantation procedure costs.
    - The applicability of these studies to the US healthcare system is unclear.
- **CRPS:** Three good quality CUAs[36,86,91] conducted outside of the U. S. compared SCS + CMM with CMM alone for treatment of CRPS.
  - All concluded that SCS + CMM was more cost-effective than CMM alone based on usual willingness to pay thresholds.
  - Two modeled a 15-year time horizon, one modeled a 20-year horizon. All note a concern about the lack of high-quality long-term data on benefits, harms, and costs to support long-term modeling. Discussion of potential biases and their impact on findings was limited across the studies.
  - The applicability of these studies to the US healthcare system is unclear.
- **PDN**: One good quality CUA conducted in the Netherlands[146] compared SCS with best medical therapy for peripheral diabetic neuropathy
  - SCS was not cost-effective over the short term due to the substantial initial costs of SCS although it was considered more effective.
  - Cost-effectiveness was sensitive to baseline cost imbalances; the impact of imputing missing data was unclear.
  - The applicability of this study to the US healthcare system is unclear.

Detailed analysis

Low back pain, FBSS

US studies: FBSS, back pain: Two U.S. based studies, one in patients with FBSS and another in patients with nonsurgical refractory back pain (NSRBP) met inclusion criteria. Appendix Table E7 contains details related to the quality rating and Appendix Table I1 details related to study characteristics and results.

Hollingworth 2011

Study overview: This good quality study[70] (QHES 90/100) evaluated the cost-effectiveness of SCS in a Washington State Workers' Compensation population (costing year: 2007) in patients with FBSS. It was funded by the Washington State Department of Labor and Industries (LNI). Effectiveness data from a 2010 prospective, 24-month cohort study[164] (N=158) included in this and the prior review that compared SCS with pain clinic evaluation (PC, based on multidisciplinary evaluation, with or without treatment) and usual care (UC). Treatment decisions were left to the patient and their providers for all groups.

Patients were currently receiving work time loss compensation, had pain radiating to one or both legs, leg pain greater than back pain with average leg pain >6 (0-10 scale) in the previous month and 1 to 3 prior open lumbar surgeries prior to their Worker's Compensation claim. In the cohort study, SCS and CMM groups were similar in demographic characteristics (i.e., age, sex, and other characteristics). At baseline, groups had similar mean medical and productivity loss costs. At baseline, the SCS group has slightly higher mean leg pain scores versus PC and UC groups (0-10 scale, 7.7 vs. 7.3 vs. 7.2), longer median pain duration (48 vs. 31 vs. 36 months) and longer median work time loss compensation (39 vs. 24 vs. 30 months). SCS recipients also had slightly higher RDQ scores (0-24 scale, 21.1 s. 201. Vs. 20.0) and were more likely to have legal representation (49% vs. 26 % vs. 29%). The primary outcome measure of benefit was a composite measure for success that included improvement of baseline scores of ≥50% for leg pain intensity, ≥2 points on the RDQ and less than daily opioid use. Success on VAS leg pain and RDQ were also used individually to evaluate benefit. Actual reimbursement and productivity loss costs were obtained from LNI databases. A 24-month time horizon was evaluated. Logistic regression, Bayesian methods and bootstrapping were used to compare 24-month costs and cost-effectiveness. Authors report unadjusted estimates of cost-effectiveness and estimates adjusted for baseline and other covariates, each with confidence interval (CI) or credibility intervals (CrI) and provide cost-effectiveness acceptability. Costs were discounted at 3% after 12 months; results are reported in 2007 USD. Of the patients who had undergone trial SCS, 53% (27/51) received permanent implants. Incremental cost per success for the primary outcome, for leg pain and RDQ were calculated. Subgroup analyses comparing those who did and didn't get implants were conducted.

Base case and sensitivity analyses: Only a small proportion of patients in the SCS, PC and UC groups achieved success on the primary (composite) outcome at 24 months (5% vs. 4% vs. 10% respectively) and differences between groups were not statistically significant. Over 24 months, adjusted total costs (medical and productivity loss) for SCS ($99,438) were substantially higher versus both PC and UC. Incremental costs of SCS were $20,074 (95% CrI, $3840 to 35,990) versus PC and 29,358 (95% CrI, $16,070 to 43,790) versus UC. The incremental cost of SCS per patient achieving success on the primary composite outcome was high compared with both PC ($131,146, 95% CrI, SCS dominates-$271,075) and UC ($334,704, 95% CrI, $142,203–489,243); substantial range in estimates is noted. These values indicate that SCS is not cost effective at commonly considered WRT thresholds of either $50,000 or $100,000.) Cost-effectiveness acceptability curve analyses (CEAC) adjusted for baseline covariates indicate that UC had >95% probability of cost-effectiveness and a low probability of PC or SCS being cost-effective. The probability that SCS would be cost-effective for the primary outcome was <5% and was <7% for a 50% reduction in VAS leg pain. The probability that SCS is cost effective did not exceed 20% even at WTP of $250,000 for ≥2 point RDQ improvement. In analyses using patients with permanent SCS implants the incremental cost of SCS per successful outcome also exceeded $100,000 for all three outcomes.

Limitations: Characteristics of this Worker's Compensation population may differ from other populations; authors note that, in general, Worker's Compensation claimants may have worse outcomes following treatments for pain compared with other populations[64,95]. Thus, the applicability of these findings to other populations is unclear. Authors also note that fewer patients had a successful SCS trial (53%) in the prospective cohort compared with what may be reported in RCTs. Sensitivity analyses were not well described. While data from a nonrandomized cohort were used, authors used various methods

to adjust for baseline differences and potential confounders. Small sample size is noted as a limitation and may contribute to the wide confidence intervals and credibility intervals.

Patel 2022

Study overview: This industry-funded, poor-quality study[124] (QHES 60/100) evaluated the cost-utility analysis of high frequency 10-kHz SCS plus CMM (n=83) versus CMM (n=76) alone for the treatment of nonsurgical refractory back pain (NSRBP). It was referred to as chronic refractory axial low back pain. This CUA is based on data from a fair-quality, multi-center RCT included in this review[78]. Authors considered pain to be refractory when CMM had failed to reach treatment goals, including inadequate pain reduction and/or improvement or if it resulted in intolerable adverse events. The population consisted of patients who were not considered to be surgical candidates based on presentation or underlying pathology (80%) or had declined surgery or were at moderate to high surgical risk (20%) based on spin surgeon evaluation prior to randomization. Of the 83 patients randomized to 10-kHz SCS who had an SCS trial, 83.1% had a permanent SCS implantation (n=69). At baseline, the proportion of female patients in the 10-kHz SCS group is higher (60.2%) versus the CMM group (52.6%). The average opioid daily dose (in morphine milligram equivalents) is higher in the 10-kHz SCS group (45.4%) than in the CMM group (32%). Other baseline characteristics between the HF-SCS and CMM groups were similar. Pain etiology was attributed to degenerative disc disease (70%) and spondylosis (65%) and radiculopathy (43%), lumbar facet-mediated pain (31%), and mild/moderated spinal stenosis (30%) with less than 10% of pain attributed to internal disc disruption/annular tear, spondylolisthesis, and sacroiliac dysfunction. Patients may have had more than one pain etiology. Mean scores at baseline were similar between groups including pain (VAS), disability scores (ODI), and utility scores (EQ-5D-5L). Components of CMM might include medications, physical therapy, and various interventional procedures as determined by the investigator tailored to the individual patient. Patients in both groups had the option to cross over to the other treatment arm at the 6-month follow-up. None of the SCS patients in the 10-kHz SCS group crossed over to the CMM group at 6 months while 86.6% elected to cross over from the CMM group to the 10-kHz SCS group. We focus here on the period prior to crossover (0-6 months) for which there are comparative data. Effectiveness outcome components included VAS, ODI, EQ-5D 5-level QOL, PGIC, daily opioid, healthcare utilization and medication usage. Total average costs were calculated for each treatment group at different time periods (i.e., at 0-6 months and 6-12 months for the CMM group, 10-kHz SCS group and the crossover group). Medication costs and the highest frequency health care utilization (HCU) components were listed and include physician visits (pain management and primary care), injection therapy (e.g., steroids), lead and IPG revision or reposition and lead or IPG explanation based on data from the RCT. Other adverse events were not described (e.g., infection). Authors only evaluated initial and short-term benefits for immediate HCU and mediation usage. Device cost, initial SCC trial and implantation costs were excluded from primary analyses.

Base case and sensitivity analyses: The ICER for 10-kHz SCS therapy was significantly below the willingness-to-pay threshold of $50,000/QALY. The 10-kHz SCS (HF-SCS) was considered the dominant strategy compared with CMM, predominantly due to a significant increase in QALY. HF-SCS was the dominant treatment versus CMM in the first 6 months (prior to crossover) with a base-case ICER of -$2,236/QALY at a WTP of $50,000/QALY and project an ICER of -$4964/QALY at 12 months for the comparison. These estimates are based on primary analyses which excluded device cost, initial SCC trial and implantation costs. The author's model including these costs suggests an ICER of over $200,000 at 6

months and approximately $100,000 QALY at 12 months (estimated from author's figure) when a mean cost of $30,000 for reimbursement for initial SCS and procedure costs is assumed. Authors state that cost-effectiveness can be achieved within 2.1 years when these costs are included and assuming QOL and medication use stay stable. Authors do not provide information on how this was determined or for a range of possible values.

Authors list the highest frequency HCU components, however it is unclear how costs and rates for such components, particularly adverse events (e.g., lead or IPG revision, removal, repositioning) were modeled. Such rates may impact long-term cost-effectiveness. Authors report reduction in HCU and medication costs for CMM patients who did receive HF-SCS after the 6 months.

Formal sensitivity analyses around modeling assumptions were not described. Authors suggest medication cost as a possible driver of cost, noting that neuromodulating pain medications and narcotics were primary drivers for medication cost but do not report formal sensitivity analyses around this or the impact that may be expected on ICER estimates. Authors' supplemental material shows lower average HCU costs for HF-SCS versus CMM ($656.31 at 6 months vs. $983.89), however changes in average medication costs at 6 months did not differ; authors attribute this to higher average daily opioid does at baseline for the HF-SCS arm vs. CMM. Supplemental material shows reduction in medication and HCU costs pre- and post-crossover for crossover patients.

Limitations: Authors only evaluated initial and short-term benefits for immediate HCU and medication usage. Main assumptions of the model are not well described. Primary analyses do not include device cost, trial cost and related procedural costs. The CPT codes for each patient visit were not recorded and were estimated for the purpose of this study. Limited analyses around changes and potential drivers of cost were available but the impact on ICERs and formal sensitivity analyses were not described. Modeling of adverse events is not well described. (Large studies included for harms as part of this update review report explant rates ranging from 4% to 27% for example.) Data comparing HF-SCS directly with continued CMM are only available up to 6 months. In the absence of longer-term data on benefits but also related to revisions, explants etc., caution regarding conclusions about continued cost-effectiveness of HF-SCS is warranted. The RCT may have been underpowered to detect rare adverse effects. Author-reported relationships with SCS manufacturer are noted.

Non-US studies for FBSS: Four CUAs conducted outside of the U.S. evaluated the cost effectiveness of SCS plus CMM with CMM alone in patients with FBSS. Three were of good quality, one was poor quality. Two[36,91] of the studies also evaluated SCS cost effectiveness in patients with CRPS; only findings for FBSS are described here. Appendix Table E8 contains details related to the quality rating and Appendix Tables I2 and I3 details related to study characteristics and results.

Rojo 2021

Study overview: this poor to fair-quality cost-utility study[134] (QHES 73/100) conducted in Spain (SP) evaluated the cost-effectiveness of SCS+CMM to CMM in patients with FBSS (N=86) over 5 years. Clinical data and utility (EQ-5-D) and cost data from a 24-month nonrandomized study of intervention (NRSI) (SEFUDOCE)[125] with follow-up visits up to 24 months of adults with FBSS who were either treated with SCS + CMM or CMM were used. Patients received either a conventional tonic SCS or higher frequency

stimulation (1000 Hz) SCS. To extrapolate beyond the 24 months to the 5-year time horizon, authors modeled an average of costs and utilities observed in the second year of the study. Cost data from the NRISI included primary care and specialty providers, ambulatory care, emergency care, ambulatory care, hospital care, diagnostic visits, interventions (not specified) and medications. Costs Additional cost data were obtained from NHS/Madrid taxes and drug cost database. At baseline, the consumption of opioids, sedatives, anticonvulsants, and antidepressants was higher for the SCS+CMM group than the CMM group and authors note the SCS+CMM group were on average 7.78 years younger than those in the SCS group. Medication consumption decreased for both treatments during the 2-year observational period. At 24 months, the level of medication consumption for the SCS group fell slightly below or similar to the CMM group. From the baseline period to 24 months, the level of medication consumption reduced for the SCS group by more than half. National Health Service (NHS, Spain) perspective and costing year of 2019 were used. Costs and outcomes were discounted using a 3% rate; results were reported in 2019 EUR; outcomes also appear to have been discounted. This study was funded by Axentiva Solutions SL.

Base case and sensitivity analyses: SCS was found to be cost-effective treatment compared to CMM in patients with FBSS, reporting an ICER of € 27,330 at 5 years which is within a WTP threshold of €30,000. Authors performed sensitivity analyses using bootstrapping with replacement calculating the mean cost and utility over time for each of the 10,000 bootstrap subsamples. SCS had a 79% probability of being cost-effective when considering a €30,000 WTP threshold. That probability would drop to 51.7% given a €20,000 WTP threshold. Based upon the assumption of the device longevity (i.e., ~12 years), the authors extended their analyses to 12 years. Based on this study's estimates and given a €30,000 WTP threshold, SCS had a 75.5% probability of being cost-effective in patients with FBSS if treatment is at 4.5 years.

Limitations: Although it was not quantified in this CUA, the authors reported that lost to follow-up was significantly greater within the CMM group during the observational period of up to 24 months. This study extrapolated the 24-months results for the subsequent years up until the 5-year period. Modeling of device and implantation costs or costs related to an SCS trial phase are not evident. Modeling or consideration of specific adverse events, need for device replacement or explant, etc. were not described. Sensitivity analyses regarding assumptions or potential drivers of either cost or effectiveness were not described. Authors mentioned a statistically significant difference in age between the SCS and CMM groups (i.e., the SCS patients were 7.78 years younger than CMM patients). It is unclear to what extent these differences were considered or adjusted for in analyses although the authors mentioned that this could have a potential impact on comparative results, but do not describe how it may have impacted results. Patients with FBSS in both CMM and SCS groups were treated based on medical conditions and not randomized, thus the impact of non-specific effects, including any potential placebo effect on patient reported outcomes is unclear as is the potential for selection bias and confounding by indication. The applicability of the findings to the U.S. healthcare system are unclear.

Deloitte 2019

Study overview: This good quality CUA[36] (QHES 90/100) evaluated the cost-effectiveness of SCS devices compared to usual care (UC) and reoperation from a health care system and societal perspective using a hypothetical cohort of patients with FBSS. Published literature informed clinical inputs for the probability of SCS trial success and complications; the size and quality of the studies was not described. In addition, modeling is partly based on care pathways developed in consultation with the

Neuromodulation Society of Australia and New Zealand, Painaustralia and the Faculty of Pain Medicine, Australia and New Zealand College of Anaesthetists. Authors assumed that complication rates were low and were likely to be short-lived and thus patients would spend a relatively short period of time in a related health stated. EQ-5D values used to measure utilities and health status came from previously published SCS economic modeling studies. The probability of trial success used in this study was assumed to be 82.7%.

A Markov simulation model (i.e., 1 year cycle length) was used. The annual transition probabilities for the model for patients in FBSS were based upon previously published literature:

- SCS optimal health state with a probability of 58.5% (i.e., patients reaching a ≥50% pain reduction from baseline VAS scores):
    - SCS optimal (probability of 90.4%)
    - SCS suboptimal (probability of 4%)
    - UC optimal (probability of 0.4%)
    - UC suboptimal (probability of 4.3%)
    - Death (probability of 0.9%)
- UC suboptimal health state with a probability of 41.5% (i.e., patients reaching a 50% pain reduction from baseline VAS scores):
    - SCS optimal (probability of 91.4%)
    - SCS suboptimal (probability of 3%)
    - UC optimal (probability of 0.4%)
    - UC suboptimal (probability of 4.3%)
    - death (probability of 0.9%)

Utility gained as reported in this study was higher for the SCS group than in the UC group for both the optimal and suboptimal health states.

Costs for SCS trial stimulation, implantation, explantation, and ongoing costs were included in modeling for SCS. Ongoing costs for UC and related to repeat operation and additional imaging were modeled for the suboptimal care pathway. Sources for costs included data from public and private hospitals in Australia from the National Hospital Cost Data Collection and Private Hospital Data Bureau annual report. Expert opinion was used as well published literature. This study was conducted in Australia and New Zealand in patients with FBSS using a 15-year time horizon. Costs were discounted using a 5% rate; costing year was not reported. The analysis was prepared for the Australian and New Zealand Neuromodulation Society Limited.

Base case and sensitivity analyses: The ICER from a health system perspective was $15,070 AUD/QALY gained, and AUD -$11,902/QALY gained from a societal perspective for SCS versus UC. When comparing SCS to UC, costs savings for SCS in patients with FBSS were higher for the SCS group when reaching 5 years or more. This study found that SCS dominated UC.

A sensitivity analysis was performed considering different time horizons (i.e., 2, 5 or 10 years), different discount rates (i.e., 3 or 7%), different ongoing cost levels of SCS/UC therapy, and different SCS device longevity (i.e., 5 or 7 years). The results from the sensitivity analysis show that:

- ICERs from a health system perspective ranged from a low of $7,335 AUD/QALY to $97,896 AUD/QALY

- a higher probability of achieving SCS optimal (i.e., 75%) while holding the costs/patient per year constant, increases the utility (QALY), increases the ICER from a health system perspective, and decreases the ICER from a societal perspective.
- The higher the time horizon, the higher the utility and the higher the ICERS from both a health system and a societal perspective. ICERs obtained with a 10-year time horizon are much higher than those at the base case scenario and the utility has also been reduced.
- Compared to a higher discount rate i.e., 7%), a lower discount rate (i.e., 3%) would keep the ICERs at a lower level and would increase the utility compared to the base case scenario.
- Having the UC utility at 90% of the SCS utility, while holding the cost/patient per year constant, decreases the ICER from a health system perspective and increases the ICER from a societal perspective.
- Increasing the SCS ongoing costs, while holding the utility constant, would also increase the ICERs from both health system and societal perspectives.
- Increasing the device longevity increases both ICERs from both a health system and a societal perspective compared to the base case scenario.

The only parameters reducing the ICERs or increasing the utility from both a health system and a societal perspective compared to the base case scenario are: a lower discount rate (i.e., 3 %), a higher probability of achieving SCS optimal (i.e., 75%), a trial success probability of 90%, or a 20% reduction the SCS ongoing costs.

Limitations: This study was a theoretical simulation of a hypothetical cohort with inputs from published literature and expert opinion. The authors did not include any deterministic probability analysis including a willingness-to-pay threshold and a cost-effectiveness acceptability curve for the SCS treatment in FBSS. The authors mentioned a 15-year time horizon although the sensitivity analysis only reports the 10-year results. The simulation assumes that any adverse events are likely short-lived; the impact of explanation, revision or replacement is somewhat unclear. Authors do not discuss limitations of the analyses such as potential sources of bias and possible impact of these on the direction and magnitude of their findings. Population characteristics are not described so applicability to a range of patients with FBSS is unclear. The applicability of the findings to the U.S. healthcare system are unclear.

Annemans 2014

Study overview: This fair cost-utility study[9] (QHES 81/100) conducted in the United Kingdom (UK) evaluated the cost-effectiveness of 10 kHz high-frequency SCS (HF10 SCS) to CMM and reoperation in patients with FBSS (N=66) and based on simulated cohort of 1000 patients over 15 years in patients with FBSS. Mean age of patients with FBSS in the study is 49.7 years old and proportion of male patients is 45%. Authors used decision modeling and a Markov chain analysis (i.e., 3-month cycles) to model and predict patients' transition from one state to another. Decision modeling included treatment failure/success and transition state included use of second line therapies, which depended initial arm (e.g., initial CMM, transition to SCS), degree of pain relief and death. Authors provide information on modeling of adverse events including complications and replacement rates from prior published sources. The authors reproduced the 2008 UK National Institute of Health and Clinical Excellence (NICE) study which assessed the cost effectiveness of traditional non rechargeable SCS (TNR-SCS) versus

conventional medical management (CMM) and reoperation in patients with FBSS. Cost data, complication costs, reoperation costs and baseline utilities came from previously published SCS economic modeling studies. Data from 24-month follow-up of patients with HF SCS implants was also included in the model[7]. HF (10 kHz) SCS therapy outcomes from this study compare favorably to traditional SCS therapy in patients with FBSS. After 24 months of the HF10 SCS therapy, 60% of patients reported a significant reduction in back pain (≥50% reduction in pain VAS scores) and 71% of patients reported a significant reduction in leg pain. Mortality rates are assumed to be the same across all groups. All costs have been discounted at 3.5%. Funding source has not been reported by the authors. The UK NHS perspective was used. The ICERs from the 2008 NICE study were as follows assuming a device longevity of 4 years and an initial cost of TNR-SCS of £9,000: £10,480/QALY gained versus CMM alone and £9,219/QALY gained versus repeat operation.

Base case and sensitivity analyses: Author's analysis suggests that HF-SCS may be cost-effective compared with both CMM alone and with reoperation. Authors reported the following ICERs: £3,153/QALY gained versus CMM and £2,666/QALY gained versus reoperation (i.e., lower than a £20,000 WTP threshold). Sensitivity analyses showed that device longevity and device cost followed by the response rate are the main drivers in the case of SCS therapy versus CMM and reoperation while follow-up costs hardly change and hardly have any impact on the ICER/QALY gained in the case SCS treatment (while holding all the other covariates constant). Authors report that for HF SCS to dominate, the percentage of patients sustaining ≥50% pain relief at 6-months needs to be 60%.

Limitations: A long time horizon (15 year) is employed. The extent to which source data for sustained effectiveness and safety extend beyond 12 to 24 months is unclear. Rates of reoperation and replacement over time may change and impact cost-effectiveness. Authors note a lack of comparative data on HF-SCS versus CMM or other treatment options. Data from a variety of sources resulted in indirect comparisons of the treatment options and adjustment for baseline factors was not done; the quality of studies used for clinical and other data is unclear. Study funding and potential conflicts of interest were not reported. The applicability of the findings to the U.S. healthcare system are unclear.

Kumar 2013 (FBSS)

Study overview: This good-quality cost utility analysis[91] (QHES 86/100) evaluated the cost-effectiveness of SCS+CMM (n=184) compared to CMM alone (n=49) in Canada for patients with FBSS over a 20-year time horizon. The study evaluated cost-effectiveness for both FBSS as well as CRPS, the former of which is reported in this section. Data from a patient database (case series data) for clinical outcomes and cost were used. Cost data was also obtained from the author's hospital finance department and neuromodulation clinic. Cost for SCS implant and trial, maintenance, use of adjunctive therapy and medication are included. For CMM costs for healthcare professional evaluation, imaging, adjunctive therapies, medications, and intermittent hospitalization for acute breakthrough pain were described. Demographic characteristics were similar in both the SCS treatment group and the CMM group. Proportion of male patients in the SCS and CMM groups were similar (64% versus 61%). The mean age of patients in the SCS group is 49 years old (versus 50 years old in the CMM group). At baseline, the mean VAS score in the SCS group is 8.2 (same as in the CMM group). At 6 months, the mean VAS score in the SCS group is 4.5 (versus 6.7 in the CMM group). At baseline, the mean utility value (as measured by the

EQ-5D) in the SCS group is 0.28 (versus 0.29 in the CMM group). At 6 months, the mean utility value in the SCS group is 0.60 (versus 0.33 in the CMM group).

This study used a decision tree model (SCS + CMM trial vs. CMM alone) and a 50,000 Markov simulation model (6-month cycles) over 20 years with the following phases after SCS implantation: optimal health state (i.e., 50% pain relief from baseline) with a probability of 60%, suboptimal health state with a probability of 30%, and death with a probability of 0.8%. The probability in the model of transitioning from SCS suboptimal health state to a CMM suboptimal health state is 70%, and the probability of transitioning from SCS suboptimal health state to a CMM optimal health state is 20%.

Costs and benefits were discounted at 3.5% rate per year beyond the first year; results were reported in 2012 CAN. As this study was conducted from a Canadian provincial Ministry of Health perspective, only direct medical costs have been considered in this study. The study was funded by Mitacs, a not-for-profit organization funded though Canadian federal and provincial governments.

Base case and sensitivity analyses: The ICER for SCS versus CMM for patients with CRPS from a Canadian provincial Ministry of Health perspective was CAN$ 9,293/QALY gained (per patient). Authors performed both deterministic (i.e., one-way) and probabilistic sensitivity analyses. The results from the probabilistic sensitivity analyses show that the 50,000 simulations over 20 years form a tight cluster. The probability of SCS being cost-effective is 75% given a WTP threshold of $50,000/QALY gained. This study also used a different an additional indicator (i.e., incremental net monetary benefit) defined as: [(QALY gained x WTP) – Cost] to evaluate the effectiveness of SCS therapy over CMM over a 20-year time horizon. For patients with FBSS, the incremental net monetary benefit is CAN$ 116,057 given a WTP threshold of $50,000/QALY gained over a 20-year time horizon. Authors calculated a strategy selection frequency showing that, in the case of patients with FBSS, in 80% of the simulations SCS therapy maximized QALYs (versus 20% for CMM). This study also included a one-way sensitivity analysis showing the range in the SCS therapy's ICER when varying the base-case value of a designated variable from its lower limit to its upper limit, while keeping the other input parameters' values constant. The following variables, ranked in order, were identified as the main drivers having the greatest impact in magnitude on the ICER for patients with FBSS:

- probability of achieving an optimal health state with SCS,
- probability of obtaining a suboptimal health state with SCS
- probability of achieving a suboptimal health state with CMM after a failed SCS trial
- probability of achieving an optimal health state with CMM after a failed SCS trial

Limitations: Case series data from a single institution were used and there is a lack of long-term head-to-head comparative data for modeling a 20-year time horizon. Although authors describe that complications were modeled, the impact of complications such as SCS revision replacement or explant and device lifetime are not clear particularly over the long term. Detailed discussion of potential sources of bias and their impact on the cost-effectiveness of SCS vs. CMM was not provided although authors note that use of nonrandomized data may lead to the possibility of treatment effect overestimation and selection bias. The applicability of the findings to the U.S. healthcare system are unclear.

Non-US studies: CRPS

A total of three studies evaluated SCS cost-effectiveness in patients with CRPS[36,86,91]. Two of the studies also evaluated SCS cost effectiveness in patients with CRPS; only findings for CRPS are described here.[36,91] Appendix Table E8 contains details related to the quality rating and Appendix Table I4 details related to study characteristics and results.

Deloitte 2019

Study overview: This good quality cost utility study[36] (QHES 90/100) evaluated the cost-effectiveness of SCS devices compared to usual care (UC) including reoperation both from a health care system and societal perspective in patients with CRPS. This study also evaluated the cost-effectiveness of SCS for FBSS and details of study methods are described above. As with the FBSS analysis, a Markov simulation model (i.e., 1 year cycle length) with the following phases was used. The probability of SCS trial success used in this study was assumed to be 82.7%. The annual transition probabilities for patients with complex regional pain syndrome (CRPS) were based upon previously published literature:

- SCS optimal health state with a probability of 58.5% (i.e., patients reaching a ≥50% pain reduction from baseline VAS scores):
    - SCS optimal (probability of 90.4%)
    - SCS suboptimal (probability of 4%)
    - UC optimal (probability of 0.4%)
    - UC suboptimal (probability of 4.3%)
    - Death (probability of 0.9%)
- UC suboptimal health state with a probability of 41.5% (i.e., patients reaching a ≤50% pain reduction from baseline VAS scores):
    - SCS optimal (probability of 91.4%)
    - SCS suboptimal (probability of 3%)
    - UC optimal (probability of 0.4%)
    - UC suboptimal (probability of 4.3%)
    - death (probability of 0.9%)

Costs for SCS trial stimulation, implantation, explanation and ongoing costs were included in modeling for SCS. Ongoing costs for UC and ketamine infusions for 2% of CRPS patients in the SCS arm and 20% of CRPS patients in the UC arm).

Base case and sensitivity analyses: The ICER from a health system perspective was AUD $2,321/QALY gained, and minus AUD $18,868/QALY gained from a societal perspective. When comparing SCS to UC, cost savings for SCS in patients with CRPS were higher for the SCS group when reaching 4 years or more. This study found that SCS dominates UC from a societal perspective.

A sensitivity analysis was performed considering different time horizons (i.e., 2, 5 or 10 years), different discount rates (i.e., 3 or 7%), different ongoing cost levels of SCS/UC therapy, and different SCS device longevity (i.e., 5 or 7 years). The results from the sensitivity analysis show that:

- ICERs from a health system perspective ranged from -$4114 AUD/QALY to $73,833 AUD/QALY
- a higher probability of achieving SCS optimal relief (i.e., 75%) while holding the costs / patient per year constant, increases the utility (QALY) and decreases the ICER from both a health system and a societal perspective.
- Compared to a higher discount rate i.e., 7%), a lower discount rate (i.e., 3%) would keep the ICERs at a lower level and would increase the utility compared to the base case scenario.
- Having the UC utility at 90% of the SCS utility, while holding the cost / patient per year constant, decreases the ICER from a health system perspective and increases the ICER from a societal perspective.
- Decreasing the SCS ongoing costs by 20%, while holding the utility constant, would lower the ICERs from both a health system and a societal perspective.
- Increasing the device longevity (i.e., to 7 years) increases both ICERs from both a health system and a societal perspective compared to the base case scenario.

The only parameters reducing the ICERs or increasing the utility from both a health system and a societal perspective compared to the base case scenario are: a lower discount rate (i.e., 3 %), a higher probability of achieving SCS optimal (i.e., 75%), a trial success probability of 90%, or a 20% reduction the SCS ongoing costs.

Limitations: The same general limitations described for the FBSS analysis apply here. This study was a theoretical simulation of a hypothetical cohort with inputs from published literature and expert opinion. Population characteristics are not described so applicability to a range of patients with CRPS is unclear. Authors do not discuss limitations of the analyses such as potential sources of bias and possible impact of these on the direction and magnitude of their findings. The applicability of the findings to the U.S. healthcare system are unclear.

Kumar 2013

Study overview: This good-quality cost utility analysis[91] (QHES 86/100) evaluated the cost-effectiveness of SCS+CMM (n=42) compared to CMM alone (n=11) in Canada for patients with CRPS over a 20-year time horizon. The study evaluated cost-effectiveness for both FBSS as well as CRPS, the latter of which is reported in this section. Data from a patient database (case series data) for clinical outcomes and cost were used. Cost data was also obtained from the author's hospital finance department and neuromodulation clinic. Cost for SCS implant and trial, maintenance, use of adjunctive therapy and medication are included. For CMM costs for healthcare professional evaluation, imaging, adjunctive therapies, medications and intermittent hospitalization for acute breakthrough pain were described. Demographic characteristics were similar in both the SCS treatment group and the CMM group. Proportion of male patients in the SCS and CMM groups were similar (52% versus 56%). The mean age of patients in the SCS group is 51 years old (versus 50 years old in the CMM group). At baseline, the mean VAS score in the SCS group is 8.1 (versus 8.2 in the CMM group). At 6 months, the mean VAS score in the SCS group is 4.1 (versus 6.9 in the CMM group). At baseline, the mean utility value (as measured by the EQ-5D) in the SCS group is 0.30 (versus 0.32 in the CMM group). At 6 months, the mean utility value in the SCS group is 0.57 (versus 0.28 in the CMM group).

This study used a decision tree model (SCS + CMM trial vs CMM alone) and a 50,000 Markov simulation model (6-month cycles) over 20 years with the following phases after SCS implantation: optimal health state (i.e., 50% pain relief from baseline) with a probability of 65%, suboptimal health state with a probability of 28%, and death with a probability of 0.8%. The probability in the model of transitioning from SCS suboptimal health state to a CMM suboptimal health state is 69%, and the probability of transitioning from SCS suboptimal health state to a CMM optimal health state is 22%.

Costs and benefits were discounted at 3.5% rate per year beyond the first year; results were reported in 2012 CAN. As this study was conducted from a Canadian provincial Ministry of Health perspective, only direct medical costs have been considered in this study. The study was funded by Mitacs, a not-for-profit org funded though CA federal and provincial governments.

Base case and sensitivity analyses: The ICER for SCS versus CMM for patients with CRPS from a Canadian provincial Ministry of Health perspective was CAN$ 11,216/QALY gained. Authors performed both deterministic (i.e., one-way) and probabilistic sensitivity analyses. The results from the probabilistic sensitivity analyses show that the 50,000 simulations over 20 years form a tight cluster. The probability of SCS being cost-effective is 87% given a WTP threshold of $50,000/QALY gained. This study also used a different indicator (i.e., incremental net monetary benefit) defined as: [(QALY gained x WTP) – Cost] to evaluate the effectiveness of SCS therapy over CMM over a 20-year time horizon. For patients with CRPS, the incremental net monetary benefit is CAN$ 172,592 given a WTP threshold of $50,000/QALY gained. This study also included a one-way sensitivity analysis showing the range in the SCS therapy's ICER when varying the base-case value of a designated variable from its lower limit to its upper limit, while keeping the other input parameters' values constant. The following variables, ranked in order, were identified as the main drivers having the greatest impact in magnitude on the ICER for patients with CRPS:

- probability of achieving an optimal health state with SCS,
- probability of obtaining a suboptimal health state with SCS
- probability of achieving a suboptimal health state with CMM after a failed SCS trial
- probability of achieving an optimal health state with CMM after a failed SCS trial

Limitations: Case series data from a single institution were used and there is a lack of long-term head-to-head comparative data for modeling a 20-year time horizon. Although authors describe that complications were modeled, the impact of complications such as SCS revision replacement or explant and device lifetime are not clear particularly over the long term. Detailed discussion of potential sources of bias and their impact on the cost-effectiveness of SCS vs. CMM was not provided although authors note that use of nonrandomized data may lead to the possibility of treatment effect overestimation and selection bias. The applicability of the findings to the U.S. healthcare system are unclear.

Kemler 2010

Study overview: This good-quality CUA[86] (QHES 79/100) conducted in the United Kingdom (UK) evaluated the cost-effectiveness of SCS to CMM (or CMM + reoperation) in patients with complex regional pain syndrome (CRPS) over 15 years from the perspective of the UK National Health Services (NHS) (costing year: 2008). Authors used data from two randomized controlled trials (RCTs) and updated

the UK National Institute of Health and Clinical Excellence (NICE) cost-effectiveness analysis. Costs were discounted using a 3.5% rate; results were reported in 2008 GBP.

Authors performed a simulation using a population of male and female patients with CRPS type I aged between 18 and 65 years old. Inclusion criteria included leg or hand pain for at least 6 months, and a pain intensity of at least 5 cm on the 100-mm VAS ratings (i.e., 0 to 4 mm can be considered as "no pain", 5 to 44 mm as "mild pain", 45 to 74 mm as "moderate pain", and 75 to 100 mm as "severe pain"). This study developed a decision tree model showing the initial 6-month responses to SCS and Markov simulation model (i.e., 3-month Markov cycles) over 15 years with the following phases: optimal pain relief (i.e., patients reaching a ≥50% pain reduction from baseline VAS scores), optimal pain relief and complications, suboptimal pain relief (i.e., patients reaching a ≤50% pain reduction from baseline VAS scores), suboptimal pain relief and complications. Authors used a 66.7% probability of trial success that came from a previously published literature. Probabilities related to SCS implantation, pain relief and complication rates also came from previously published literature. Mean utility values derived from the EuroQoL/EQ-5D questionnaire were 0.195 for no pain relief, 0.581 associated with optimal pain relief. The study was sponsored by Medtronic.

Base case and sensitivity analyses: The ICER of SCS versus CMM from the UK NHS perspective was £3,562 / QALY gained. Results in this study show that the probability of SCS being cost-effective is 87% given a WTP threshold of £30,000.

Authors performed a probabilistic sensitivity analysis (PSA) using a 1000 Monte Carlo simulation. The covariates used in the sensitivity analysis were probabilities of clinical success, reoperation, and death, probabilities of achieving optimal and suboptimal pain reliefs, complication rates, costs and drug treatments, utilities of health states, and SCS failure rates over time. Each model input parameter was varied around its mean (i.e., 95% confidence intervals, expert opinions, or minimum and maximum values) using appropriate distributions (i.e., beta, gamma distributions). Results of the PSA show that the probability of SCS being cost-effective is 87% given a WTP threshold of £30,000, and 74% given a WTP threshold of £20,000.

Authors also performed a one-way sensitivity analysis showing the range in the SCS therapy's ICER when varying the base-case value of a designated variable from its lower limit to its upper limit, while keeping the other input parameters' values constant. Results from the one-way sensitivity analysis show that the cost-effectiveness of SCS increases and the ICER would then decrease as:

- the cost of adjunct drug pain therapy (base case: £1,692) for SCS patients decreases (i.e., leading to an SCS dominant position versus CMM when the ICER falls below £0, and the cost of adjunct pain therapy for SCS patients is less than £1,197 per patient)
- the time before a replacement IPG (base case: 4 years) is needed increases (i.e., ICER would be higher than the £3,562/QALY gained at base case but still lower than the £20,000 WTP threshold. SCS becomes dominant economically when the time before a replacement IPG is 7 years or more)
- the cost of drug therapy (base case £2,664) in CMM patients increases (i.e., SCS becomes dominant economically when the cost of drug therapy in CMM per patient is higher than £4,645)
- the annual probability of no pain relief with SCS decreases

The estimates of cost-effectiveness of SCS in the base-case analysis appeared to be robust across all ranges of the one-way PSA, those results remain below the £20,000 WTP threshold.

Limitations: There is a lack of long-term head-to-head comparative data for costs, benefits and harms for modeling the long-term (15-year) time-horizon. Authors reported that the cost of SCS screening was constant across all patients, and drug medication was not recorded. This study sourced health care costs from another study (i.e., PROCESS study) conducted for patients in FBSS and not for patients with a CRPS condition. It is unclear how longer-term events such as revision or explant may affect long-term cost-effectiveness. The applicability of the findings to the U.S. healthcare system are unclear.

PDN

Slangen (2017) *This study was in the form of an unedited manuscript that had been accepted for publication*

Study overview: This good-utility study[146] (QHES 81/100) evaluated the cost-effectiveness of SCS+BMT treatment compared to best medical treatment alone (BMT) in patients (N=36) with painful diabetic peripheral neuropathy (PDPN) in the lower limbs over 12 months, and both from a health care system and societal perspective in the Netherlands. Costs were discounted using a 4% rate; results were reported in 2012 EUR.

Clinical data from the lead authors RCT. Main inclusion criteria for the patients with PDPN were pain over 12 months, a pain intensity greater or equal to 5 (NRS scale), and previously unsuccessful treatment. 39% of patients with PDPN were in the BMT controlled group while 61% of the patients with PDPN were in the SCS treatment group; out of which 77% had an SCS implantation (i.e., 17 patients in PDPN had a successful trial). This study reported that there were no statistically significant differences between the two groups at baseline. The average age was 57.1 years old in the SCS group and 56.5 years old in the BMT group. The utility scores (pooled mean) measured by the EQ-5D were 0.25 at baseline, 0.51 at 3 months, 0.46 at 6 months, 0.49 at 9 months and 0.48 at 12 months in the SCS group. In the BMT group, the utility scores (pooled mean) were 0.33 at baseline, 0.43 at 3 months and 0.33 at 6 months. The calculated QALYs were 0.50 in the SCS treatment group and 0.36 in the BMT group. This study also reported the Michigan Diabetic Neuropathy Score (MDNS) (i.e., 0=no neuropathy, 1=mild neuropathy, 2=moderate neuropathy, and 3=severe neuropathy), and other characteristic demographics such as level education (i.e., low, middle, high) and employment status (i.e., retired, employed, unemployed, incapacitated, domestic work). Appendix Table E8 contains details related to the quality rating and Appendix Table I5 details related to study characteristics and results.

Base case and sensitivity analyses: At 12 months, ICERs from a health system perspective were €34,519/patient, and €94,160/QALY gained from a societal perspective. The probability for the SCS treatment to be cost-effective given a €80,00 WTP threshold/QALY gained ranged from 0% to 46%. In the short run, SCS treatment is not cost-effective. This study found that SCS is more costly and more effective than BMT depending on the WTP threshold from a societal perspective.

Authors performed bootstrap analyses (with 1000 simulations), sensitivity analyses and corrected for imbalances found in the covariates to counterbalance an overestimation of the ICERs. As costs were not normally distributed, differences between the SCS and BMT groups were addressed using non-parametric bootstrapping with 95% confidence intervals around mean costs and effects of the

treatment group and the controlled group. To account for the battery life and longevity of the device, the SCS cost was depreciated over 4 years instead of 1 year.

Compared to the base case scenario, results from the sensitivity analyses with a 4-year depreciation period indicated a lower ICER at a lower WTP threshold/QALY gained (i.e., a reduced ICER of €62,775/QALY gained from a societal perspective given a WTP threshold/QALY nearly twice lower than the base case).As only 6 months of data were available for the BMT group (versus 12 for the SCS treatment), authors performed a sensitivity analysis over a 6-month period to compare results in both groups. With a 6-month time horizon, the sensitivity analyses showed an ICER of €117,815/QALY gained from a societal perspective. Authors also extrapolated data over a 4-year time horizon. After extrapolating at 1 year and combining it with a 4-year SCS cost depreciation, the ICER was €62,775/QALY gained (i.e., lower than the base case scenario). At 4 years and with a 4-year SCS cost depreciation, the ICER was at €52,252 / QALY gained (i.e., still lower than the base case scenario).

Limitations: Study source of funding was reported. However, there might be some potential conflicts of interest as the manufacturer provided a grant for the employment of one researcher for up to 3 years. Data was collected retrospectively which could affect data accuracy. This study only had 6 months of data for the BMT group which were extrapolated to 12 months to be compared to the 12 months of observations from the SCS treatment group (e.g., a 6-month success rate in the BMT group was used as a 12-month success rate in patients with PDPN). Results in this study from a health care perspective, were from an extrapolation of data up to 4 years (based on 24 months of data from the SCS treatment and 6 months of data from the BMT group) with the assumption that the proportions of successfully treated patients remained constant over time. Patients with missing data were retained in the analysis. The applicability of the findings to the U.S. healthcare system are unclear.

5 Strength of Evidence (SOE)

The following strength of evidence (SOE) summaries have been based on the highest quality of studies available across the totality of the evidence identified from the prior report and this update report. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by time frame and/or comparator. Details of other outcomes are available in the report.

Notes: Only primary outcomes (function, pain, opioids, serious adverse events) were rated for SOE

5.1 Strength of Evidence Summary: Efficacy Results

5.1.1 Strength of Evidence Summary: Efficacy Results from Crossover Trials comparing SCS with sham (placebo) in patients with FBSS or persistent radicular pain following low back surgery

Outcome	Crossover phases, time	Studies N (randomized)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS vs. Sham Effect estimate (95% CI) Conclusion	Quality (SoE)
Function: ODI (0-100 scale)	2, 12-week phases per intervention	1 RCT (N=50) Hara	No	Unknown	No	No	Burst vs. sham **Mean, 95%CI** 34.0 (95% CI 30.0 to 38.1) vs. 35.4 (95% CI 31.3 to 39.4) **Δ from baseline** -10 (95% CI -14 to 7.2) vs. -9.3 (95% CI -12.7 to -5.9) **MD in change scores:** -1.3 (95% CI -3.9 to 1.3, p=0.32) Conclusion: Similar functional improvement between burst SCS and sham	⊕⊕⊕◯ MODERATE

Outcome	Crossover phases, time	Studies N (randomized)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS vs. Sham Effect estimate (95% CI) Conclusion	Quality (SoE)
Back pain VAS or NRS (0-10 scale)	2, 12-week phases per intervention	Burst vs. Sham 1 RCT (N=50) Hara 2022	No	Unknown	No	No	Burst vs. sham **Mean, 95% CI** 5.9 (95% CI 5.3 to 6.4) vs. 6.1 (95% CI 5.6 to 6.6) **MD** −0.2 (95% CI −0.7 to 0.2), p=0.32 <u>Conclusion</u>: Similar back pain improvement between burst SCS and sham	⊕⊕⊕◯ MODERATE
	For 4, 3-week phases (over 12 weeks)	Multiple frequencies vs. sham 1 RCT (N=24) Al-Kaisy 2018	Yes(-1)	Unknown	No	Yes (-1) (CI includes range from small effect to large effect)	**<u>Mean (SD), range:</u>** **1200 Hz**: 4.51 (1.87), range 0.07 to 7.03; **3030 Hz**: 4.57 (2.09), range 0.10 to 8.77 **5882 Hz:** 3.22 (1.98), range 0 to 6.30; **Sham:** 4.83 (2.45), range 0 to 9.43 Author reported P-value *across groups*, p=0.002 **MD (95%CI) calculated from data provided** 1200 Hz vs. Sham: MD -0.32 (-1.59 to 0.94) 3030 Hz vs. Sham: MD -0.26 (-1.58 to 1.06) 5882Hz vs. Sham: MD -1.61 (-2.67 to -0.55) (author-reported MD appears to be adjusted, but no CI reported; CI	⊕◯◯◯ INSUFFICIENT

Outcome	Crossover phases, time	Studies N (randomized)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS vs. Sham Effect estimate (95% CI) Conclusion	Quality (SoE)
							here was calculated from authors reported p-value) **Calculated MD from Cochrane (95% CI)*** 1200 Hz vs. Sham: MD -0.32 (-2.17 to 1.54) 3030 Hz vs. Sham: MD -0.26 (-2.1 to 1.63) 5882 Hz vs. Sham: MD-1.61(-3.48 to 0.26) Conclusion: Evidence in insufficient to draw conclusions.	
Leg pain (0-10 scale)	2, 12-week phases per intervention	Burst vs. Sham 1 RCT (N=50) Hara 2022	No	Unknown	No	Yes (-1)	Burst vs. sham Mean (95% CI) 5.9 (5.3 to 6.4) vs. 6.1 (5.6 to 6.6), MD, −0.2 (95% CI −0.7 to 0.2), p=0.32 Conclusion: Similar leg pain improvement between burst SCS and sham	⊕⊕◯◯ LOW
	For 4, 3-week phases (over 12 weeks)	Multiple frequencies vs. sham 1 RCT (N=24) Al-Kaisy 2018	Yes (-1)	Unknown	No	Yes (-2) (variability NR)	Mean (SD or CI) Baseline: 3.06 (NR) Sham: 2.51 (NR) 1200 Hz: 2.37 (NR) 3030 Hz: 2.20 (NR) 5882 Hz: 1.81 (NR) P across groups = 0.367 Conclusion: Evidence is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Crossover phases, time	Studies N (randomized)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS vs. Sham Effect estimate (95% CI) Conclusion	Quality (SoE)
VAS Pain (NOS, 0-10 scale)	4, 2-week periods per intervention	1 RCT (N=18) Sokal 2020	Yes (-2)	Unknown	No	Yes (-2)	Observed mean (SD) **1000 Hz:** 5.17(1.42) **LF Tonic:** 4.18 (1.76) **Cluster Tonic:** 5.27(1.33) **Sham:** 5.42(1.22) **Unadjusted MD (95% CI)** 1000 Hz : MD -0.25 (95% CI -1.15 to 0.65) LF tonic MD -1.24 (95% CI -2.27 to -0.21) Cluster tonic: MD -0.15 (95% CI, --1.01 to 0.71) **Adjusted MD (95% CI)*** 1000 Hz: -0.17 (-0.77 to 0.43) LF tonic: -0.99 (-2.25 to 0.27) Cluster tonic: -0.03(-1.06 to 1.0) Conclusion: Evidence from this poor-quality trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT

CI = Confidence interval; FBSS = Failed back surgery syndrome; HF = High frequency; Hz = Hertz; IPG= internal pulse generator; LF = Low frequency; MD = Mean difference; ODI = Oswestry Disability Index; RCT = randomized controlled trial; NOS = not otherwise specified; NRS = Numerical rating scale; SCS = Spinal cord stimulation; SD = Standard deviation; SOE = Strength of Evidence; VAS = Visual analogue scale.

* Based on Traeger 2023 Cochrane review[162] which adjusted for repeated measures on participants

5.1.2 Strength of Evidence Summary: Efficacy Results from Parallel Trials Comparing SCS versus CMM for Chronic Back Pain – FBSS or NSRBP

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
Pain Responders – LBP (≥50% reduction in LBP on the VAS/NPRS (0-10))	3 mos.	**HF (10 kHz)-SCS** 1 RCT (N=159) Kapural, 2022 NSRBP ITT analysis	Yes (-1)	Unknown	No	Yes (-2)	**HF (10 kHz)-SCS** 74.3% (62/83) vs. 1.3% (1/76); RR 56.77 (95% CI 8.07 to 399.46) <u>Conclusion</u>: HF SCS was associated with a substantial increase in the likelihood of achieving LBP versus CMM alone in patients with NSRBP however, the effect estimate was extremely imprecise.	⊕⊕◯◯ LOW
	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=140) Kapural, 2022 NSRBP PP analysis **Conv. SCS** 1 RCT (N=218) Rigoard, 2019 FBSS ITT analysis	Yes (-1)	Unknown	No	Yes (-2)	**HF (10 kHz)-SCS** 80.0% (52/65) vs. 2.7% (2/75); RR 30.00 (95% CI 7.60 to 118.38) **Conv. SCS** 13.6% (15/110) vs. 4.6% (5/108); RR 2.95 (95% CI 1.11 to 7.82) <u>Conclusion:</u> Both types of SCS were associated with a substantial increase in the likelihood of achieving LBP response versus CMM	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
							alone. The magnitude of effect was much larger for the HF (10 kHz)-SCS in patients with NSRBP however, effect estimates were extremely imprecise.	
	24 mos.	**Conv. SCS** 1 prospective NRSI (N=52) Perez, 2021	Yes (-1)	Unknown	No	Yes (-1)	36% (10/29) vs. 4% (1/23), RR 7.9 (95% CI 1.09 to 57.52) **≥30% reduction in PD-Q scores** 48.7% (19/33) vs. 8.7% (4/25), RR 5.6 (95% CI 1.40 to 22.00) Conclusion: Evidence from this trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Pain Responders – Leg pain (≥50% reduction in leg pain on the VAS/ NPRS (0-10))	3 mos.	**Conv. SCS** 1 RCT (N=94) Kumar 2007 FBSS ITT analyses	Yes (-1)	Unknown	No	Yes (-1)	56.0% (28/50) vs. 9.1% (4/44); RR 6.16 (95% CI 2.34 to 16.19) Conclusion: SCS associated with a large increase in the likelihood of achieving leg pain response versus CMM alone in patients with FBSS	⊕⊕◯◯ LOW
	6 mos.	**Conv. SCS** 2 RCTs (N=312) Rigoard, 2019 Kumar 2007 FBSS	Yes (-1)	No	No	Yes (-1)	**RCTs:** 35.6% (57/160) vs. 8.6% (13/152); RR 4.09 (95% CI 2.11 to 8.63), I^2=0%	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		ITT analyses 1 prospective NRSI (N=155) Turner, 2010 FBSS Worker's compensation	Yes (-1)	Unknown	No	Yes (-2)	**NRSI:** 18% (9/51) vs. 3% (2/66) (usual care) vs. 5% (2/38) (pain clinic) **vs. usual care** (N=117): RR 5.82 (95% CI 1.32 to 25.79) **vs. pain clinic** (N=89): RR 3.35 (95% CI 0.77 to 14.63) <u>Conclusion:</u> Conventional SCS associated with a large increase in the likelihood of achieving leg pain response versus CMM alone in patients with FBSS.	
	12, 24 mos.	1 prospective NRSI (N=148, 12 mos.; N=138, 24 mos.) Turner, 2010 FBSS Worker's compensation	Yes (-1)	Unknown	No	Yes (-1)	**12 months** 15% (7/47) vs. 17% (11/65) (usual care) vs. 8% (3/36) (pain clinic) **vs. usual care** (N=112): RR 0.88 (95% CI 0.37 to 2.10) **vs. pain clinic** (N=89): RR 1.79 (95% CI 0.50 to 6.43) **24 months** 16% (7/43) vs. 21% (13/61) (usual care) vs. 15% (5/34) (pain clinic) **vs. usual care** (N=104): RR 0.76 (95% CI 0.33 to 1.76) **vs. pain clinic** (N=77): RR 1.11 (95% CI 0.39 to 3.18)	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
							Conclusion: Similar proportions of patients in the SCS vs. usual care and pain clinic groups achieved pain response.	
Pain Scores – LBP (VAS/ NPRS (0-10))	3 mos.	**HF (10 kHz)-SCS** 1 RCT (N=143) Kapural, 2022 NSRBP PP analysis **Conv. SCS** 1 RCT (N=94) Kumar 2007 FBSS ITT analyses	Yes (-1)	Unknown	No	No	**HF (10 kHz)-SCS** MD -5.31 (95% CI -5.88 to -4.75) **Conv. SCS** MD -1.00 (95% CI -1.49 to -0.51) Conclusion: Both types of SCS were associated with improvement in back pain scores versus CMM alone but the magnitude of effect differed; the improvement was large with HF SCS and small with conventional SCS.	⊕⊕◯◯ LOW
	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=140) Kapural, 2022 NSRBP PP analysis **Conv. SCS** 2 RCTs (N=312) Rigoard, 2019 Kumar 2007 FBSS	Yes (-1)	Unknown	No	No	**RCTs** **HF (10 kHz)-SCS** MD -5.57 (95% CI -6.25 to -4.90) **Conv. SCS** MD -1.18 (95% CI -1.76 to -0.57), I^2=0% Conclusion: Both types of SCS were associated with improvement in back pain	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		ITT analysis					scores versus CMM alone but the magnitude of effect differed; the improvement was large with HF SCS and moderate with conventional SCS.	
	12, 24 mos.	1 prospective NRSI (N=148, 12 mos.; N=138, 24 mos.) Turner, 2010 FBSS Worker's compensation 1 prospective NRSI (N=52) Perez, 2021 FBSS with radiculopathy	Yes (-1)	Yes (-1)	No	Yes (-1)	**NRSI (FBSS, workers' compensation)** <u>12 months</u> **vs. usual care:** MD 0.5 (95% CI -0.3 to 1.3) **vs. pain clinic**: MD -0.4 (95% CI -1.3 to 0.5) <u>24 months</u> **vs. usual care:** MD 0.5 (95% CI -0.3 to 1.3) **vs. pain clinic**: MD 0.0 (95% CI -0.7 to 0.7) **NSRI (FBSS with radiculopathy)** VAS pain at present moment: MD -2.05, p≤0.01 PD-Q total: MD -4.78, p=0.05 <u>Conclusion</u>: Evidence is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Pain Scores – Leg pain (VAS/ NPRS (0-10))	3 mos.	**Conv. SCS** 1 RCT (N=94) Kumar 2007 FBSS	Yes (-1)	Unknown	No	No	MD -3.30 (95% CI -3.86 to -2.73) <u>Conclusion:</u> Conventional SCS associated with a large	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		ITT analyses					improvement in leg pain scores versus CMM alone in patients with FBSS and radiculopathy (and leg pain greater than back pain).	
	6 mos.	**Conv. SCS** 2 RCTs (N=312) Rigoard, 2019 Kumar 2007 FBSS ITT analysis 1 prospective NRSI (N=155) Turner, 2010 FBSS Workers' compensation	Yes (-1)	No	No	Yes (-1)	MD -1.82 (95% CI -3.68 to -0.16), I^2=82.6% **Leg pain *less* than back pain** 1 RCT, N=218 (Rigoard, 2019): MD -1.20 (95% CI -1.84 to -0.56) **Leg pain *greater* than back pain (all had radiculopathy)** 1 RCT, N=94 (Kumar, 2007): MD -2.67 (95% CI -3.69 to -1.65) **NRSI** **vs. usual care:** adjusted MD 0.3 (95% CI -0.5 to 1.0) **vs. pain clinic**: adjusted MD 0.8 (95% CI -0.1 to 1.7) Conclusion: Conventional SCS was associated with a moderate improvement in leg pain in pooled analysis; however, heterogeneity was substantial, possibly due to the difference in patient populations: one trial enrolled patients whose leg	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
							pain was less than their back pain and reported a small improvement favoring SCS and the other trial included patients with radiculopathy whose leg pain was greater than their back pain and reported a large improvement in pain with SCS.	
	12, 24 mos.	1 prospective NRSI (N=148, 12 mos.; N=138, 24 mos.) Turner, 2010 FBSS Workers' compensation	Yes (-1)	Unknown	No	Yes (-1)	**12 months** **vs. usual care:** adjusted MD -0.6 (95% CI -1.3 to 0.2) **vs. pain clinic**: adjusted MD 0.6 (95% CI -0.2 to 1.3) **24 months** **vs. usual care:** adjusted MD -0.2 (95% CI -1.0 to 0.6) **vs. pain clinic**: adjusted MD 0.4 (95% CI -0.6 to 1.3) Conclusion: Evidence from this study is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Function responders: (≥10 point reduction in ODI score (0-100))	3 and 6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=143 at 3 mos.; N=140 at 6 mos.) Kapural, 2022 NSRBP PP analysis	Yes (-1)	Unknown	No	Yes (-1)	**3 months** **RCT:** 80.9% (55/68) vs. 12.0% (9/75); RR 6.74 (95% CI 3.61 to 12.58) **6 months** **RCT:**	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		1 prospective NRSI (N=155) Turner, 2010 FBSS Workers' compensation					78.5% (51/65) vs. 4.0% (3/75); RR 18.75 (95% CI 6.13 to 57.31) **NRSI:** (≥ 2-point improvement on RDQ) 41% (21/51) vs. 32% (21/66) (usual care) vs. 29% (11/38) (pain clinic) **vs. usual care** (N=117): RR 1.3 (95% CI 0.8 to 2.1) **vs. pain clinic** (N=89): RR 1.4 (95% CI 0.8 to 2.6) Conclusion: At both timepoints, HF SCS was associated with a substantial increase in the likelihood of achieving function response in patients treated for NRSBP; the estimate at 6 months was very imprecise.	
	12, 24 mos.	1 prospective NRSI (N=148, 12 mos.; N=138, 24 mos.) Turner, 2010 FBSS Worker's compensation	Yes (-1)	Unknown	No	Yes (-1)	**≥ 2-point improvement on RDQ:** **12 months** 32% (15/47) vs. 48% (31/65) (usual care) vs. 36% (13/36) (pain clinic) **vs. usual care** (N=112): RR 0.67 (95% CI 0.41 to 1.09)	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
							vs. pain clinic (N=89): RR 0.88 (95% CI 0.48 to 1.61) **24 months** 51% (22/43) vs. 44% (27/61) (usual care) vs. 41% (14/34) (pain clinic) **vs. usual care** (N=104): RR 1.16 (95% CI 0.77 to 1.73) **vs. pain clinic** (N=77): RR 1.24 (95% CI 0.76 to 2.04) Conclusion: Evidence from this study is insufficient to draw conclusions	
Function scores (ODI (0-100))	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=140) Kapural, 2022 NSRBP PP analysis **Conv. SCS** 2 RCTs (N=312) Rigoard, 2019 Kumar 2007 FBSS ITT analysis 1 NRSI (N=155) Turner, 2010 FBSS	Yes (-1)	Unknown (HF) No (Conv.)	No	Yes (-1)	**HF (10 kHz)-SCS** MD -22.70 (95% CI -25.98 to -19.42) **Conv. SCS** MD -7.61 (95% CI -14.43 to -2.45), I^2=20.1% **NRSI** **vs. usual care:** adjusted MD 1.2 (95% CI 0.0 to 2.4) **vs. pain clinic**: adjusted MD 1.1 (95% CI -0.2 to 2.4) Conclusion: Both types of SCS were associated with improvement in ODI scores versus CMM alone but the	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		Workers' compensation					magnitude of effect differed; the improvement was substantial with HF SCS and small with conventional SCS.	
	12, 24 mos.	1 prospective NRSI (N=148, 12 mos,; N=138, 24 mos.) Turner, 2010 FBSS Workers' compensation 1 prospective NRSI (N=52) Perez, 2021 FBSS with radiculopathy	Yes (-1)	Yes (-1)	No	Yes (-1)	**1 NRSI, RDQ (0-24)** Workers' compensation **12 months** **vs. usual care:** adjusted MD 0.2 (95% CI -1.2 to 1.6) **vs. pain clinic**: adjusted MD 0.4 (95% CI -1.2 to 2.0) **24 months** **vs. usual care:** adjusted MD 0.1 (95% CI -1.6 to 1.7) **vs. pain clinic**: adjusted MD 0.5 (95% CI -1.4 to 2.4) **1 NRSI, ODI (0-100)** **24 months** MD -8.52, p>0.05 Conclusion: Evidence from these studies is insufficient to draw conclusions	⊕◯◯◯ INSUFFICIENT
Opioid use (proportion of patients still using opioids)	6 mos.	**Conv. SCS** 2 RCTs (N=290) Rigoard, 2019 As treated analysis Kumar 2007	Yes (-1)	No	No	Yes (-1)	62.8% (81/129) vs. 76.4% (123/161); RR 0.84 (95% CI 0.68 to 1.01), I^2=0% Conclusion: SCS associated with a small decrease the	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		ITT analysis FBSS ITT analyses 1 prospective NRSI (N=52) Perez, 2021 FBSS with radiculopathy					likelihood of continued opioid use versus CMM alone in patients with FBSS.	
	12-24 mos.	1 prospective NRSI (N=148, 12 mos,; N=138, 24 mos.) Turner, 2010 FBSS Workers' compensation 1 prospective NRSI (N=52) Perez, 2021 FBSS with radiculopathy 2 propensity score-matched database studies (N=69,201) Dhruva, 2023 Vu, 2022	Yes (-1)	Yes (-1)	No	No	**<u>12 months</u>** **1 NRSI (workers' compensation)** 85% (40/47) vs. 71% (46/65) (usual care) vs. 75% (27/36) (pain clinic) **vs. usual care** (N=112): RR 1.20 (95% CI 0.99 to 1.46) **vs. pain clinic** (N=83): RR 1.13 (95% CI 0.91 to 1.42) **1 database study (n=7,560)** **chronic opioid use:** 54.9% vs. 51.8%; adjusted OR, 1.14 (95% CI 1.01 to 1.29), **long-acting opioid use** 22.5% vs. 18.5% adjusted OR 1.28 (95% CI 1.11 to 1.49), **high MME dose:** 64.7% vs. 50.3%, adjusted OR 1.81 (95% CI 1.60 to 2.04)	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
							<u>24 months</u> **1 NRSI (workers' compensation)** 84% (36/43) vs. 71% (43/61) (usual care) vs. 74% (25/34) (pain clinic) **vs. usual care** (N=104): RR 1.19 (95% CI 0.96 to 1.46) **vs. pain clinic** (N=77): RR 1.14 (95% CI 0.89 to 1.45) **1 NRSI (FBSS radiculopathy)** 31% (n=NR) vs. 25% (n=NR), p=0.72 **<u>15 months</u>** **1 database study (N=64,641)** <u>≥6 prescriptions/year</u> (primarily analysis): OR 0.93 (95% CI to 0.87 to 0.98) <u>Conclusion</u>: Evidence from this study is insufficient to draw conclusions.	
Opioid use (proportion with change in opioid use)	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=140) Kapural, 2022 NSRBP PP analysis	Yes (-1)	Unknown	No	Yes (-1)	**Stopped opioid use entirely** 22% (16/65) vs. 0% (0/75), p<0.05 **Decreased opioid use** 44% (27/65) vs. 17% (13/75), RR 2.40 (95% CI 1.35 to 4.25) **Increased opioid use**	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
							6% (4/65) vs. 49% (37/75), RR 0.12 (95% CI 0.05 to 0.33) **Stable opioid dose** 28% (18/65) vs. 34% (26/75), RR 0.80 (95% CI 0.48 to 1.32) <u>Conclusion:</u> Substantially more HF SCS patients decreased opioid use or stopped altogether, and fewer patients increased opioid use compared with CMM. Similar proportions of patients in both groups remained on a stable opioid dose.	
Opioid use (mean MME dose)	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=74) Kapural, 2022 NSRBP PP analysis **Conv. SCS** 2 RCTs (N=312) Rigoard, 2019 As treated analysis Kumar 2007 ITT analysis FBSS	Yes (-1)	Yes (-1)	No	Yes (-1)	**HF (10 kHz)-SCS** MD -18.70 (95% CI -28.61 to -8.79) **Conv. SCS** MD -10.14 (95% CI -59.87 to 25.56), I^2=0% <u>Conclusion:</u> Evidence is considered insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT

CI = Confidence interval; CMM = conventional medical management; Conv. = conventional; FBSS = Failed back surgery syndrome; HF = High frequency; ITT = intention to treat; kHz = Kilohertz; LBP = low back pain; MD = Mean difference; MME = morphine milligram equivalents; mos. = months; NOS = not otherwise specified; NPRS = Numerical pain rating scale; NRSI = nonrandomized studies of interventions; NSRBP = Nonsurgical refractory back pain; ODI = Oswestry Disability Index; PP = per protocol/completers; RCT = randomized controlled trial; RDQ = Roland Morris Disability Questionnaire; RR = risk ratio; SCS = Spinal cord stimulation; SD = Standard deviation; SOE = Strength of Evidence; VAS = Visual analog scale.

5.1.3 Strength of Evidence Summary: Efficacy Results from Parallel Trials Comparing SCS versus Reoperation for FBSS

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS vs. Reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
Treatment "success": *pain relief ≥50%* (outcome measure used NR) and *patient satisfaction* (would have treatment again).	Mean 2.9 years	**Conv. SCS** 1 RCT (N=45) North, 2005 FBSS	Yes (-1)	Unknown	No	Yes (-1)	47% (9/19) vs. 12% (3/26); RR 4.11 (95% CI 1.28 to 13.16) Conclusion: Evidence from this trial is insufficient to draw conclusions	⊕◯◯◯ INSUFFICIENT
Opioid use (proportion on a stable or decreased dose of opioid medications)			Yes (-1)	Unknown	No	Yes (-1)	87% (20/23) vs. 58% (15/26); RR 1.51 (95% CI 1.05 to 2.17) Conclusion: Evidence from this trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT

CI = Confidence interval; FBSS = Failed back surgery syndrome; RCT = randomized controlled trial; RR = Risk ratio; SCS = Spinal cord stimulation; SOE = Strength of Evidence.

5.1.4 Strength of Evidence Summary: Efficacy Results from Crossover Trials comparing SCS with sham (placebo) in patients CRPS

Outcome	Crossover phases, time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS vs. Sham Effect estimate (95% CI) Conclusion	Quality (SoE)
VAS Pain (0-10 scale)	2 weeks per setting over a 10-week period with a 2-day washout period	1 RCT (N=29) Kriek 2016	Yes (-1)	Unknown	No	Yes (-1)	Author reported P across groups = 0.001 SCS vs. sham **Unadjusted MD (95%CI)** 40 Hz SCS: -2.39 (-3.57 to -1.22) 500 Hz SCS: -2.36 (-3.58 to -1.15) 1200 Hz SCS: -2.08 (-3.27 to -0.89) Burst SCS: -1.58 (-2.84 to -0.31) **Adjusted MD (95%CI)*** 40 Hz SCS: -2.39 (-4.35 to -0.43) 500 Hz SCS: not calculated 1200 Hz SCS: -2.08 (-4.1 to -0.06) Burst SCS: -1.5 (-3.79 to 0.65) Conclusion: Evidence from this small trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
McGill NRS average pain (0-10 scale)	2 weeks per setting over a 10-week period with a 2-day	1 RCT (N=29) Kriek 2016	Yes (-1)	Unknown	No	Yes (-1)	Author reported P across groups = 0.001 SCS vs. sham **Unadjusted MD (95%CI)** 40 Hz SCS: -2.37 (-3.35 to -1.39)	⊕◯◯◯ INSUFFICIENT

Outcome	Crossover phases, time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS vs. Sham Effect estimate (95% CI) Conclusion	Quality (SoE)
	washout period						500 Hz SCS: -1.97 (-3.03 to -0.91) 1200 Hz SCS: -1.76 (-2.84 to -0.68) Burst SCS: -1.41 (-2.54 to -0.28) <u>Conclusion</u>: Evidence from this small trial is insufficient to draw conclusions.	

CI = Confidence interval; CRPS = Complex regional pain syndrome; HF = High frequency; Hz = Hertz; IPG= internal pulse generator; LF = Low frequency; MD = Mean difference; ODI = Oswestry Disability Index; RCT = randomized controlled trial; NOS = not otherwise specified; NRS = Numerical rating scale; SCS = Spinal cord stimulation; SD = Standard deviation; SOE = Strength of Evidence; VAS = Visual analogue scale.
* Based on O'Connell Cochrane review which adjusted for repeated measures on participants

5.1.5 Strength of Evidence Summary: Efficacy Results from Parallel Trials Comparing SCS versus CMM or PT for CRPS

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or PT Effect estimate (95% CI) Conclusion	Quality (SoE)
Pain Scores (VAS/NRS (0-10))	3 mos.	**HF (10 kHz)-SCS** 1 RCT (N=29) Canos-Verdecho, 2021 ITT analysis **Conv. SCS** 2 RCTs (N=85)	Yes (-1)	No	No	Yes (-1)	**HF (10 kHz)-SCS** MD -3.50, 95% CI -5.10 to -1.90 **Conv. SCS** MD -2.60 (95% CI -3.70 to -1.50) [Kemler 2004, N=54] MD -3.40 (95% CI -4.73 to -2.07) [Canos-Verdecho, 2021, N=31]	**10 kHz SCS** ⊕◯◯◯ INSUFFICIENT **Conv. SCS** ⊕⊕◯◯ LOW (based on fair quality)

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or PT Effect estimate (95% CI) Conclusion	Quality (SoE)
		Canos-Verdecho, 2021 (ITT analysis) Kemler, 2000 (PP analysis)					Conclusion: Conventional SCS was associated with a large improvement in pain scores vs. PT based on one fair-quality trial. Evidence from one poor-quality trial of HF (10 kHz) SCS is insufficient to draw conclusions.	
	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=29) Canos-Verdecho, 2021 ITT analysis **Conv. SCS** 2 RCTs (N=85) Canos-Verdecho, 2021 (ITT analysis) Kemler, 2000 (PP analysis)	Yes (-1)	No	No	Yes (-1)	**HF (10 kHz)-SCS** MD -1.80 (95% CI -3.21 to -0.39) **Conv. SCS** MD -2.39 (95% CI -3.39 to -1.34), I^2=0% Conclusion: Conventional SCS was associated with a large improvement in pain scores vs. PT based on one fair-quality trial. Evidence from one poor-quality trial of HF (10 kHz) SCS is insufficient to draw conclusions.	10 kHz SCS ⊕◯◯◯ INSUFFICIENT ⊕⊕◯◯ LOW (based on fair quality)
	12-24 mos.	**HF (10 kHz)-SCS** 1 RCT (N=29) Canos-Verdecho, 2021	Yes (-1)	No	No	Yes (-1)	**HF (10 kHz)-SCS** 12 mos: MD -0.80 (95% CI -2.88 to 1.28) **Conv. SCS** 12-24 mos.: MD -1.97 (95% CI -3.08 to -0.77), I^2=0%	10 kHz SCS ⊕◯◯◯ INSUFFICIENT ⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or PT Effect estimate (95% CI) Conclusion	Quality (SoE)
		ITT analysis **Conv. SCS** 2 RCTs (N=82) Canos-Verdecho, 2021 (ITT analysis) Kemler, 2000 (PP analysis)					<u>Conclusion:</u> Conventional SCS was associated with moderate improvement vs. PT based on one fair-quality trial. Evidence from one poor-quality trial of HF (10 kHz) SCS is insufficient to draw conclusions.	(based on fair quality)
	60 mos.	**Conv. SCS** 1 RCT (N=44) Kemler, 2008 PP analysis	Yes (-1)	Unknown	No	Yes (-1)	MD -0.70 (95% CI -2.47 to 1.07) <u>Conclusion:</u> Evidence from this trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Function scores (ODI (0-100))	3, 6, 12 mos.	**HF (10 kHz)-SCS** 1 RCT (N=29) Canos-Verdecho, 2021 ITT analysis	Yes (-1)	Unknown	No	Yes (-1)	**3 months** MD -2.1 (95% CI -5.66 to 1.46) **6 months** MD 8.3 (95% CI 4.54 to 12.06) **12 months** MD 11.2 (95% CI 6.23 to 16.17) <u>Conclusion:</u> Evidence from this poor-quality trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or PT Effect estimate (95% CI) Conclusion	Quality (SoE)
		Conv. SCS 1 RCT (N=31) Canos-Verdecho, 2021 ITT analysis	Yes (-1)	Unknown	No	Yes (-1)	**3 months** MD -14.2 (95% CI -18.81 to -9.59) **6 months** MD -6.1 (95% CI -10.77 to -1.43) **12 months** MD -5.0 (95% CI -9.79 to -0.21) <u>Conclusion:</u> Evidence from this poor-quality trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT

CI = Confidence interval; CMM = conventional medical management; Conv. = conventional; CRPS = Complex regional pain syndrome; HF = High frequency; ITT = Intention-to-treat; kHz = Kilohertz; MD = Mean difference; mos.= months; NRS = Numerical rating scale; ODI = Oswestry Disability Index; PP = Per protocol/completers; PT = Physical therapy; RCT = randomized controlled trial; SCS = Spinal cord stimulation; SD = Standard deviation; SOE = Strength of Evidence; VAS = Visual analogue scale.

5.1.6 Strength of Evidence Summary: Efficacy Results from Parallel Trials Comparing SCS versus CMM for PDN

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
LE Pain Responders (≥50% reduction in LE pain on the VAS/NRS (0-10))	3 mos.	**HF (10 kHz)-SCS** 1 RCT (N=184) Petersen, 2021 PP analysis	Yes (-1)	Unknown	No	Yes (-1)	88.6% (78/88) vs. 7.3% (7/96); RR 12.16 (95% CI 5.93 to 24.90) <u>Conclusion:</u> SCS was associated with a large increase in the likelihood of achieving LE pain response	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
							compared with CMM alone however, the effect estimate was imprecise.	
	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=180) Petersen, 2021 PP analysis **Conv. SCS** 2 RCTs (N=96) de Vos, 2014 Slangen, 2014 ITT analysis	Yes (-1)	No	No	Yes (-1)	**HF (10 kHz)-SCS** 85.1% (74/87) vs. 5.4% (5/93); RR 15.82 (95% CI 6.71 to 37.28) **Conv. SCS** 54.8% (34/62) vs. 2.9% (1/34); RR 12.46 (95% CI 1.94 to 79.74); I^2=0% <u>Conclusion:</u> Both types of SCS were associated with a large increase in the likelihood of achieving LE pain response compared with CMM alone however, effect estimates were imprecise.	⊕⊕◯◯ LOW
LE Pain Scores (VAS/ NRS (0-10))	3 mos.	**HF (10 kHz)-SCS** 1 RCT (N=180) Petersen, 2021 PP analysis **Conv. SCS** 1 RCT (N=36) Slangen, 2014 ITT analysis	Yes (-1)	No	No	Yes (-1)	**HF (10 kHz)-SCS** MD -4.85 (95% CI -4.91 to -4.79) **Conv. SCS** MD -3.20 (95% CI -4.58 to -1.82) <u>Conclusion:</u> Both types of SCS were associated with a large improvement in LE pain scores compared vs. CMM alone.	⊕⊕◯◯ LOW

Outcome*	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone Effect estimate (95% CI) Conclusion	Quality (SoE)
	6 mos.	**HF (10 kHz)-SCS** 1 RCT (N=180) Petersen, 2021 PP analysis **Conv. SCS** 2 RCTs (N=96) de Vos, 2014 Slangen, 2014 ITT analysis	Yes (-1)	No	No	Yes (-1)	**HF (10 kHz)-SCS** MD -5.20 (95% CI -5.26 to -5.14) **Conv. SCS** MD -3.17 (95% CI -4.49 to -1.66), I^2=12.7% Conclusion: Both types of SCS were associated with a large improvement in LE pain scores vs. CMM alone.	⊕⊕◯◯ LOW
Opioid use (proportion of patients still using opioids); **MQS III scores**	6 mos.	**Conv. SCS** 1 RCT (N=60) de Vos, 2014	Yes (-1)	Unknown	No	Yes (-1)	Proportion taking opioids 37.5% (15/40) vs. 55.0% (11/20); RR 0.68 (95% CI 0.39 to 1.20) MQS III scores MD -2.4 (95% CI -7.08 to 2.28) Conclusion: Similar proportion of patients in both groups still taking opioids; similar change in change in medication regimen between groups.	⊕⊕◯◯ LOW

CI = Confidence interval; CMM = conventional medical management; Conv. = conventional; HF = High frequency; ITT = Intention-to-treat; LE = lower extremities; kHz = Kilohertz; MD = Mean difference; mos. = months; MQS = Medication quantification scale; NRS = Numerical rating scale; PDN = Painful diabetic neuropathy; PP = Per protocol/completers; RCT = randomized controlled trial; RR = Risk ratio; SCS = Spinal cord stimulator; SD = Standard deviation; SOE = Strength of Evidence; VAS = Visual analogue scale.

5.2 Strength of Evidence Summary: Safety Results

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
Comparative evidence								
Mortality	6 mos.	**FBSS** 1 RCT (N=49) North, 2005 Conv. SCS Prospective NRSI (N=158) Turner, 2010 FBSS Workers' compensation Retrospective database (N=16,455) Lad 2014 FBSS **PDN** 1 RCT (N=36) Slangen, 2014 Conv. SCS	Yes (-1)	No	No	Yes (-2)	**RCT, FBSS:** SCS: 5.3% (1/23) vs. CMM: 0% (0/26); cardiac event near 6-month follow-up, unclear if related to SCS **Prospective NRSIs** SCS: 2.0% (1/51) vs. UC: 0% (0/68) vs. Pain Clinic: 0% (0/39); occurred between 6 and 12 months, cause not reported. **Retrospective Database** SCS: 0% (0/395) vs. Reoperation: 0.12% (20/16,060), at index visit **RCT, PDN:**	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
							SCS: 4.5% (1/22) vs. CMM: 0% (0/14); Dural puncture during implantation resulting in a large subdural hematoma leading to unresponsiveness; patient died 10 days after surgical evacuation (never regained consciousness). <u>Conclusion</u>: Evidence from these trials is insufficient to draw conclusions; trials were likely underpowered to detect rare events	
Withdrawal due to AEs	6 mos.	**CLBP** 2 RCTs (N=365) Kapural, 2022 HF (10 kHz)-SCS NSRBP	Yes (-1)	No	No	Yes (-1)	**CLBP**: 2.2% (4/182) vs. 0.5% (1/183), RR 2.49 (95% CI 0.18, 37.28), I^2=0%	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
		Rigoard, 2019 Conv. SCS FBSS **PDN** 2 RCTs (N=252) Petersen, 2021 HF (10 kHz)-SCS Slangen, 2014 Conv. SCS					**PDN:** 5.9% (8/135) vs. 1.7% (2/117); RR 2.84 (95% CI 0.52 to 16.38), I^2=0% Conclusion: The risk of withdrawal due to AEs was similar for SCS and CMM; estimates were imprecise.	
Parallel RCTs								
Any SCS-related AE	6 mos.	2 RCTs (Total N=215, N range 102 to 113) Petersen, 2021 PDN 10 kHz SCS Rigoard, 2019 FBSS Conv SCS	Yes (-1)	No	No	Yes (-1)	Total: 14.9% (32/215) Range: 12.4% to 17.6% Conclusion: In RCTs, the frequency of any SCS-related AEs ranged from 12.4% to 17.6%	⊕⊕◯◯ LOW
	12-24 mos.	3 RCTs (Total N=403, N range 84 to 174) Kapural, 2022 NSRBP	Yes (-1)	No	No	Yes (-1)	Total: 26.3% (106/403) Range: 24.1% to 32.1%	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
		10 kHz SCS Rigoard, 2019 FBSS Conv SCS Petersen, 2021 PDN 10 kHz SCS					Conclusion: The frequency of any SCS-related AEs was high (range, 24.1%– 32.1%).	
Any SCS-related AE: requiring surgery	6 mos.	2 RCTs (Total N=126, N range 24 to 102) Kemler, 2000 Rigoard, 2019 FBSS Conv SCS	Yes (-1)	No	No	Yes (-1)	Pooled: 12.7% (16/126) Range: 11.8% to 16.7% Conclusion: In RCTs, SCS-related AEs requiring surgery ranged from 11.8% to 16.7%	⊕⊕◯◯ LOW
	12-24 mos.	2 RCTs (Total N=108, N range 24 to 84) Kumar, 2007 FBSS Conv. SCS Kemler, 2004 CRPS Conv. SCS	Yes (-1)	No	No	Yes (-1)	Pooled: 26.9% (29/108) Range: 23.8% to 37.5% Conclusion: The frequency of any SCS-related AEs requiring surgery was high (range, 23.8%–37.5%).	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
	60 mos	1 RCT (N=24) Kemler, 2008 CRPS Conv. SCS	Yes (-1)	No	No	Yes (-2)	41.7% (10/24) Conclusion: Evidence from this small trial is insufficient to draw conclusions	⊕◯◯◯ INSUFFICIENT
Any SCS-related AE: serious	6 months	3 RCTs Rigoard, 2019 FBSS Conv SCS Petersen, 2021 PDN 10 kHz SCS Slangen, 2014 PDN Conv. SCS	Yes (-1)	No	No	Yes (-2)	**2 RCTs** (Total N=132, N range 113 to 19) Pooled: 3.0% (4/132) Range: 1.8% to 10.5% 1 dural puncture (led to death) 1 infection (required explant) Specifics NR by 1 RCT **1 RCT:** 13 events (patients NR); specifics not reported Conclusion: Evidence is insufficient from these trials to draw conclusions; trials were likely	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
							underpowered to detect rare events.	
	12-24 mos.	3 RCTs Rigoard, 2019 FBSS Conv SCS Kapural, 2022 NSRBP 10 kHz SCS Petersen, 2023 PDN 10 kHz SCS	Yes (-1)	No	No	Yes (-2)	**1 RCT (10 kHz SCS):** 4.1% (6/145) 2 implant site infections (requiring IPG explant and reimplantation); 1 sensory deficit (attributed to 10-kHz SCS stimulation); 1 poor wound healing (treated with device explant); 1 severe lethargy (due to narcotic use); and 1 osteomyelitis **1 RCT (10 kHz SCS):** 4.5% (7/154), specifics not provided **1 RCT (Conv. SCS):** 24 events (patients NR), specific	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
							events not specified <u>Conclusion</u>: Evidence is insufficient to draw conclusions; trials are likely underpowered to detect differences in rare or uncommon events.	
Cross over trials								
Any AE	Within 12 weeks	Burst vs. Sham 1 RCT (N=50) Hara 2022	No	Unknown	No	Yes (-1)	18% (9/50) <u>Conclusion</u>: A large percent of patients may experience an AE	⊕⊕◯◯ LOW
Other AEs	Within 12 weeks	Burst vs. Sham 1 RCT (N=50) Hara 2022	Yes	Unknown	No	Yes (-2)	Superficial infection (antibiotics) 2% (1/50) Micturition problems 2% (1/50) 0%: post-operative hematoma, pneumonia, thromboembolism,	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
							cardiovascular complication, urinary tract infection <u>Conclusion:</u> Evidence is insufficient from this trial to draw conclusions. Some of the listed AEs may be rare or uncommon; the study may not be sufficiently powered to detect them.	
Withdrawal due to AE (NOS)	Screening Device trial	Multiple frequencies vs. sham 1 RCT (N=24) Al-Kaisy 2018	Yes (-1)	Unknown	No	Yes (-1)	Screening: 1.9% (1/53) Device trial: 2.6% (1/39) <u>Conclusion</u>: Evidence is insufficient to draw conclusions. Authors do not provide reasons for withdrawal and whether they were due to SCS specifically; one	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
							may have occurred prior to device implantation.	
Serious Adverse Events	5, 2-week phases; 2-day washout between	CRPS 1 RCT (N=29) Kriek 2016	Yes (-1)	Unknown	No	Yes (-2)	Authors report that no serious AEs occurred. <u>Conclusion</u>: Evidence is insufficient to draw conclusions; the trial was likely underpowered to detect rare events	⊕◯◯◯ INSUFFICIENT
Electrode dislocation or reconfiguration			Yes (-1)	Unknown	No	Yes (-2)	Dislocation: 10% (3/29) Reconfiguration: 8 events <u>Conclusion</u>: Evidence from this small trial is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Comfortable paresthesia not reached; Pmax too high; Adjust pulse width			Yes (-1)	Unknown	No	Yes (-2)	Paresthesia: 24% (7/29) Pmax too high: 8 events Pulse width adjusted: 27 events	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
							No conclusions are drawn	
Events across study designs								
Any IPG Device Explant (author sum)	Any time range of follow-up times	5 Parallel RCTs (N range 19-154) 1 Pro NRSI (N=27) 2 Crossover RCTs (N range, 18-50) **Studies with >100 patients** 5 Case series (N range, 620-955) 2 Registry (N range, 718-1,289) Database (N range, 8,727-52,070)	Yes (-1)	Yes (-1)	No	Yes (-1)	Parallel RCTs: 1.4%-5.3% Pro NRSI: 22% Crossover RCTs: 2%-16.7% Case series: 4%-18.8% Registry: 7.6% to 25.2% Database: 6%-9% <u>Conclusion:</u> Across studies, explant frequency ranges substantially	⊕⊕◯◯ LOW
IPG removal due to malfunction	Any time range of follow-up times	**Studies with >100 patients** 2 Case series (N range, 175-298)	Yes (-1)	Unknown	No	Yes (-2)	0.3%-0.6% <u>Conclusion:</u> Evidence is insufficient from these studies to draw conclusions. This appears to be rare; studies may have been underpowered.	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
IPG removal for infection and/or dehiscence	Any time range of follow-up times	**Studies with >100 patients** Infection 5 Case series or 1 Registry (N range, 164- 2,737) Infection or dehiscence 2 Case series, (N range, 595-955)	Yes (-1)	No	No	Yes (-1)	Infection 1%-5% Infection or dehiscence 2.5%-4.8% <u>Conclusion:</u> This appears to be uncommon.	⊕⊕◯◯ LOW
IPG removal inadequate pain relief, loss of efficacy, lack of efficacy, inadequate benefit	Any time range of follow-up times	2 Parallel RCTs (N range, 134-145) 1 Crossover RCT (N=18) **Studies with >100 patients** 5 Case series: (N range, 175-955) 3 Registries (N range, 402-1,289)	Yes (-1)	Yes (-1)	No	Yes (-1)	Parallel RCTs: 0% Crossover RCT: 13% 5 Case series: 3%-20.3% Registry: 2.0% to 16.6% <u>Conclusion:</u> Across studies, removal frequency due to lack of efficacy ranges substantially	⊕⊕◯◯ LOW
Any IPG *revision or replacement* (author sum)	Any time range of follow-up times	5 Parallel RCTs (N range, 24-174) Pro NRSI (N=27) 2 Crossover RCTs (total N =68)	Yes (-1)	Yes (-1)	No	Yes (-1)	4 Parallel RCTs (N range, 84-174): 0.9% to 3.2% [after exclusion of one	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
		Comparative database (N=1,260) **Studies with >100 patients** 1 Case series (N=620) 1 Registry (N=402)					small trial, n=24, 8.3%] Pro NRSI: 11% Crossover RCTs: 2.9% Comparative database: 22% Case series: 3.1% Registry: 15.9% <u>Conclusion:</u> Frequency of revision or replacement ranges substantially	
IPG revision or replacement due to IPG displacement or migration	Any time range of follow-up times	**Studies with >100 patients** 1 Case series (N=336) 2 Registries (N range, 402- 1,289)	Yes (-1)	No	No	Yes (-1)	Case series: 1.2% Registry: 0.5%-1.2% <u>Conclusion:</u> IPG replacement or revision due to migration may be uncommon	⊕⊕◯◯ LOW
Any lead/electrode replacement or revision (author reported sum)	Any time range of follow-up times	5 Parallel RCTs (Ns 24-154) 1 Pro NRSI (N=27) 2 Crossover RCTs (N range, 18-50) 1 Comparative database (N=1260)	Yes (-1)	Yes (-1)	No	Yes (-1)	4 Parallel RCTs (N range, 31 to 154): 0.6%-10% [after exclusion of one small trial, n=24, 20.8%] Pro NRSI: 14.8%	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
		Studies with >100 patients 1 Case series (N=298) 1 Database (N=12,297)					Crossover RCTs: 5.6%-8% Comparative database: 17.9% Case series: 4.0% Registry: 3.4% <u>Conclusion:</u> Frequency of lead revision or replacement varies; across studies with greater sample size it appears to be uncommon	
Lead failure or migration (surgery not specified) Lead Fracture or failure	Any time range of follow-up times	Fracture or migration 3 Parallel RCTs (N range, 36-113) Fracture or failure **Studies with >100 patients** 5 Case series (N range, 164-527) 2 Registries (N range, 402-614)	Yes (-1)	Yes (-1)	No	Yes (-1)	**Fracture or migration** 2 RCTs: 0.9%-9.5% **Lead Fracture or failure** Case series: 3.6% - 15.8% Registry:1.1%-6.2% <u>Conclusion:</u> Frequency of these events varies	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
Serious infection, deep, fatal infection; leading to revision, removal hospitalization (not reported under removal or revision)	Any time range of follow-up times	5 Parallel RCTs (N range, 19-174 Pro NRSI (N=28) **Studies with >100 patients with >3-year f/u** 3 Case series (N range, 175-527) Registry (N=1,289) **Within 30 days** 1 Case series (N=321) Database(N=1,521)	Yes (-1)	No	No	Yes (-1)	RCTs: 1.4% to 6.0% Pro NRSI: 4% **>3 year f/u** Case series: 3.2%-3.8% Registry: 3.9% **Within 30 days** Database: 0.9% Case series: 0.4% (fatal, during trial period) <u>Conclusion:</u> Frequency of serious infection at longer follow up appears to be 1.4% to 6%. The frequency of infection may be less within 30 days of implant	⊕⊕◯◯ LOW
Unintentional durotomy, CSF leak, dural tear	Any time range of follow up times	Unintentional durotomy 1 Crossover RCT (N=50) **Studies with >100 patients**	Yes (-1)	No	No	Yes (-1)	Unintentional durotomy Crossover RCT: 6% (3/50) CSF leak, dural tear Case series: 0.6%	⊕⊕◯◯ LOW

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
		2 Case series: (N range, 164-336) Registry (N=402)					Database: 0.7% <u>Conclusion:</u> These seem to be rare events	
Neurological injury (deficit, paralysis, intraspinal abscess)	Any time range of follow up times	4 Parallel RCTs (N range, 19-145) Pro NRSI (N=28) 2 Case series (N range, 212-620) 1 Database (N=12,297)	Yes (-1)	No	No	No	3 RCTs (N range,113-145): 0%-0.7% [excluding one small trial, n=19, 5.3%] Pro NRSI: 4% Case series: 0.2%-0.9% Database: 0.2% <u>Conclusion:</u> These seem to be rare events.	⊕⊕⊕◯ Moderate
Allergic reaction or anaphylaxis	Any time range of follow up times	2 Crossover RCTs (N range, 18-50) 2 Registries: (N range, 402- 614)	Yes (-1)	Yes (-1)	No	Yes (-1)	Allergic reaction 1 Crossover RCT (N=18): 5.6% 2 Registry: 0.2%-0.7% Anaphylaxis 1 Crossover RCT (N=50): 0% <u>Conclusion:</u> Evidence is insufficient from	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	SCS (+ CMM) vs. CMM alone or reoperation Effect estimate (95% CI) Conclusion	Quality (SoE)
							this small trial to draw conclusions..	
AE requiring hospitalization	Any time range of follow up times	1 Case series (N=212) Registry (N=402) 2 Database: (N range, 1,521-12,297)	Yes (-1)	Yes (-1)	No	Yes (-2)	1 to 13 years 1 Case series: 0.9% Registry: 20.9% Database: N=12,297, 17.2% Within 30 days Database (N=1,521): 0.7% <u>Conclusion:</u> Evidence is insufficient from these studies to draw conclusions. There is substantial variation in reported frequency and heterogeneity across studies; no firm conclusions are possible.	⊕◯◯◯ INSUFFICIENT

AE = Adverse event; CI = Confidence interval; CLBP = Chronic low back pain; CSF = Cerebrospinal fluid leak; FBSS = Failed back surgery syndrome; HF = High frequency; Hz = Hertz; IPG= internal pulse generator; IPG = Implantable pulse generator; ITT = Intention-to-treat; LBP = Low back pain; LF = Low frequency; kHz = Kilohertz; MD = Mean difference; NRSI = Non-randomized study of intervention; NOS = not otherwise specified; PDN = Painful diabetic neuropathy; PP = Per protocol; Pro = prospective; PT = Physical therapy; RCT = randomized controlled trial; RDQ = Roland-Morris Disability Questionnaire; RR = Risk ratio; SCS = Spinal cord stimulation; SD = Standard deviation; SOE = Strength of Evidence.

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