Does industry funding and study location impact findings from randomised controlled trials of spinal cord stimulation? A systematic review and meta-analysis

Prof Sam Eldabe, MD;[1] Sarah Nevitt, PhD;[2] Sue Copley, MSc;[1] Michelle Maden, PhD;[2] Lisa Goudman, PhD;[3,4,5,6] Salim Hayek, MD;[7] Nagy Mekhail, MD;[8] Maarten Moens, MD;[3,4,5,9] Phillipe Rigoard, MD;[10,11,12] Rui V Duarte, PhD[2,13]

[1] Department of Pain Medicine, The James Cook University Hospital, Middlesbrough, UK

[2] Liverpool Reviews and Implementation Group, Department of Health Data Science, University of Liverpool, Liverpool, UK

[3] Department of Neurosurgery, Universitair Ziekenhuis Brussel, Brussels, Belgium

[4] Center for Neurosciences (C4N), Vrije Universiteit Brussel, Brussels, Belgium

[5] STIMULUS research group, Vrije Universiteit Brussel, Brussels, Belgium

[6] Research Foundation—Flanders, Brussels, Belgium

[7] Division of Pain Medicine, University Hospitals, Cleveland Medical Center, Cleveland, OH, USA

[8] Department of Pain Management, Cleveland Clinic, Cleveland, OH, USA

[9] Department of Radiology, Universitair Ziekenhuis Brussel, Brussels, Belgium

[10] PRISMATICS Lab (Predictive Research In Spine/neurostimulation Management and Thoracic Innovation in Cardiac Surgery), Poitiers University Hospital, Poitiers, France

[11] Department of Neurosurgery, Spine & Neurostimulation Unit, Poitiers University Hospital, Poitiers, France

[12] UPR 3346, CNRS, P0 Institute, Futuroscope, Faculty of Sciences, Poitiers, France

[13] Saluda Medical Pty Ltd, Artarmon, New South Wales, Australia

Address for correspondence: Prof Sam Eldabe, Department of Pain and Anaesthesia, The James Cook University Hospital, Murray Building, Marton Rd, Middlesbrough TS4 3BW, UK. Email: seldabe@mac.com

Word count: 4045

Funding statement: No funding was received in support of this study.

Keywords: industry funding; meta-analysis; spinal cord stimulation; systematic review

Disclosures: SE has received consultancy fees from Medtronic, Mainstay Medical, Boston Scientific, and Abbott, outside the submitted work. He has received department research funding from the National Institute of Health Research, Medtronic and Nevro. SN reports consultancy fees from Saluda Medical outside the submitted work. LG is a postdoctoral research fellow funded by the Research Foundation Flanders (FWO), Belgium (project number 12ZF622N). NM has received consulting fees from Boston Scientific, Sollis Therapeutics, Saluda Medical, Nevro, Abbott, Vertos Medical, Nuvectra, and Relievant Medsystems, outside the submitted work; is a Medical Monitor for Mainstay's RESTORE clinical trial; and has received research support from Avanos "Halyard," Mallinckrodt, Mesoblast, and Neuros Medical. MM has received speaker fees from Medtronic and Nevro, outside the submitted work. PR reports grants and personal fees from Medtronic, Abbott and Boston Scientific, outside the submitted work. RVD is an employee of Saluda Medical, the employer had no role in the submitted work. He has previously received consultancy fees from Mainstay Medical, Medtronic Ltd and Saluda Medical, outside the submitted work. All remaining authors declare no competing interests.

ABSTRACT

Background/Importance: Concerns have been raised that effects observed in studies of spinal cord stimulation (SCS) funded by industry have not been replicated in non-industry funded studies and that findings may differ based on geographical location where the study was conducted.

Objective: To investigate the impact of industry funding and geographical location on pain intensity, function, health-related quality of life and adverse events reported in randomised controlled trials (RCTs) of SCS.

Evidence Review: Systematic review conducted using MEDLINE, CENTRAL, EMBASE and WikiStim databases until September 2022. Parallel-group RCTs evaluating SCS for patients with neuropathic pain were included. Results of studies were combined in random-effects meta-analysis using the generic-inverse variance method. Sub-group meta-analysis were conducted according to funding source and study location. Risk of bias was assessed using Cochrane RoB 2.0 tool.

Findings: Twenty-nine reports of 17 RCTs (1823 participants) were included. For the comparison of SCS with usual care, test for subgroup differences indicate no significant differences (p=.48, moderate certainty evidence) in pain intensity score at 6-months for studies with no funding or funding not disclosed (pooled mean difference [MD] -1.96 [95% CI -3.23 to -0.69; 95% prediction interval [PI] not estimable, I^2=0%, Tau^2=0]), industry funding (pooled MD -2.70 [95% CI -4.29 to -1.11; 95% PI -8.75 to 3.35, I^2=97%, Tau^2=2.96) or non-industry funding (MD -3.09 [95% CI -4.47 to -1.72]; 95% PI, I^2 and Tau^2 not applicable). Studies with industry funding for the comparison of high-frequency SCS (HF-SCS) with low-frequency SCS (LF-SCS) showed statistically significant advantages for HF-SCS compared to LF-SCS while studies with no funding showed no differences between HF-SCS and LF-SCS (low certainty evidence).

Conclusion: All outcomes of SCS versus usual care were not significantly different between studies funded by industry and those independent from industry. Pain intensity score and change in pain intensity from baseline for comparisons of HF-SCS to LF-SCS seem to be impacted by industry funding.

INTRODUCTION

Spinal cord stimulation (SCS) is a recommended intervention for the management of chronic neuropathic pain conditions.[1 2] For nearly 50 years, since SCS was first described in 1967[3] until 2014, the randomised controlled trial (RCT) evidence for SCS was limited to three trials.[4-6] The last decade has seen the emergence of new stimulation paradigms and with these, an increase in the number of RCTs conducted.[7-13] Industry sponsorship and funding have been essential drivers of innovation, technological advances and evidence generation.

The influence of industry on the outcome of studies may include direct sponsorship which usually includes framing of the research question, study design and conduct, data analysis and potential selective reporting leading to inappropriate conclusions. In other cases, industry may act as funders and part collaborators of investigator-initiated trials to include provision of technical know-how or statistical analysis as well as partnership on framing the research question. Finally, some industry-funded studies are conducted without input from the funder. Sources of funding and role of funders should be reported.[14] Industry-sponsored studies of drugs or medical devices are more likely to produce results favouring the company product than non-industry sponsored studies.[15-19] Recent reviews have observed that methodological and reporting deficiencies are common in RCTs of SCS.[20 21] Further, conflicting results have been observed questioning the relative effectiveness of different stimulation paradigms,[22 23] with suggestions that industry funding may drive discrepancies in SCS outcomes.[24]

To the best of our knowledge, no previous systematic review or meta-analysis has investigated the impact of industry finding and study location (i.e., geographical location where the study was conducted) on outcomes of SCS studies. The aim of this systematic review was to investigate the impact of industry funding and study location on outcomes of pain intensity, physical function, health-related quality of life (HRQoL), adverse events and device explants reported in RCTs of SCS.

METHODS

This article focuses on evidence from parallel group RCTs of SCS. The protocol for this review was registered in PROSPERO (CRD42022332075). We did not seek publication of the protocol in a peer-reviewed journal. This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[25] No protocol changes occurred after registration of the review.

Data sources and searches

An information specialist (MM) searched Ovid MEDLINE, Cochrane Library (CENTRAL), EMBASE and WikiStim from database inception to 17 December 2021, with updated searches to 13 September 2022. Electronic database selection follows Cochrane recommendations.[26] The search strategies are presented in Supplement 1 of this manuscript. The searches were supplemented by screening reference lists of relevant systematic reviews and eligible studies.

Study selection

Studies were eligible for inclusion if they met the following criteria: i) adult patients (18 years of age or older) with chronic neuropathic pain (persistent spinal pain syndrome type 2 [PSPS-T2], complex regional pain syndrome [CRPS], painful diabetic neuropathy [PDN]), ii) evaluation of SCS (all stimulation paradigms and types of lead), iii) compared to usual care (UC) as specified in the individual studies, an active intervention or placebo, iv) reported pain intensity, physical function, HRQoL, adverse events or device explants, v) in a parallel group RCT study design, vi) any setting and vii) reported in a full-text publication. There were no language restrictions, however only English-language studies were identified. Two investigators (RVD and SC) independently reviewed abstracts and full-text articles against the prespecified eligibility criteria, using consensus with a third investigator (SE) for any disagreements.

Outcomes

The primary outcome of the reviews was pain intensity score measured using a visual analogue scale (VAS) or numeric rating scale (NRS). Secondary outcomes were change in pain intensity from baseline, the proportion of patients achieving at least 50% reduction in pain, measures of physical function, HRQoL, adverse events and device explants. The primary timepoint of interest was 6 months; all outcomes were also considered at 3 months,

12 months and last-follow-up. Where cross-over from the control group to SCS was allowed after primary study endpoint, pain, physical function and HRQoL data from the last follow-up before cross-over only were considered for inclusion in the analysis. Longer-term follow-ups of the included RCTs were assessed for reports of adverse events and device explants. Outcomes were considered as final values and as change from baseline at 3 months, 6 months, 12 months and last follow-up. Data extraction was performed by one reviewer (SC) and verified by two reviewers (RVD and SN).

Risk of bias assessment

Risk of bias (RoB) was assessed by using the revised Cochrane RoB tool (RoB 2.0).[27] RoB assessment of the included studies was undertaken by one reviewer (SC or MM) and verified for agreement by a second reviewer (RD or MM). Authors involved in the systematic review who were involved in the original studies did not assess RoB of included RCTs. Any disagreements were resolved by consensus.

Data extraction and data synthesis

Individual participant data (IPD) were available from the authors of two RCTs[28 29] meeting the inclusion criteria and data items were extracted at study level from the other eligible RCTs. Data extracted (at the study level) or available within IPD (study level or participant level) refers to study author and year of publication, country where the study was conducted, funding sources, demographic data (i.e., age, sex), diagnosis, duration of pain, intervention, comparator, duration of follow-up, and outcome data including the number of participants included in the analysis. No attempts were made to retrieve missing data from investigators. IPD were cross-checked and outcomes calculated as previously reported.[30] Additional details on data synthesis are presented in Supplement 2.

Four main comparisons were identified within the RCTs, i) SCS compared to usual care (e.g., conventional medical management [CMM], physical therapy), ii) high-frequency (HF) SCS compared low-frequency (LF) SCS, iii) SCS compared to other interventions (e.g., other types of stimulation, surgery), and iv) comparison of different modalities of SCS (e.g., closed-loop compared to open-loop SCS, SCS with or without a trial period, multicolumn compared with monocolumn). One three-armed RCT[13] comparing HF-SCS, LF-SCS and CMM was included within the comparison of SCS to usual care by splitting the control group,[31] and also the comparison of HF-SCS to LF-SCS.

Clinical heterogeneity of included studies was assessed by comparing study design characteristics, participant characteristics and definitions of outcomes.

We deemed studies to be sufficiently clinically homogenous in terms of study characteristics and population to perform a meta-analysis for comparisons of SCS compared to UC and HF-SCS compared to LF-SCS. Sufficient outcome data were reported to perform meta-analysis for these comparisons for outcomes pain intensity at 3, 6, 12-months and last follow-up, proportion of patients achieving at least 50% reduction in pain from baseline at 6-months, EQ-5D VAS score and Index score and Oswestry Disability Index (ODI) score. Outcome data available only in graphical format were extracted using WebPlot Digitizer (https://automeris.io/WebPlotDigitizer/).

The measure of treatment effect for pain intensity and HRQoL outcomes was mean difference (MD) and 95% confidence interval (CI), and for at least a 50% reduction in pain intensity was risk ratio (RR) and 95% CI. 95% prediction intervals were also presented. Random-effects meta-analysis was performed using the generic-inverse variance method, using the meta command[32] in R version 4.0.2, with restricted maximum likelihood (REML) used to estimate heterogeneity variance.[33] We assessed statistical heterogeneity in meta-analysis according to the I^2 statistic (the percentage of variability between trials that is due to statistical heterogeneity) with higher values corresponding to higher levels of statistical heterogeneity.[34]

Subgroup meta-analyses were conducted according to funding source (industry funding received or no industry funding received or declared), by location (USA, USA and the rest of the world [RoW] and RoW) and by pain diagnosis (e.g., CRPS, PSPS-T2, PDN).

A narrative synthesis was performed for outcomes and comparisons where clinical heterogeneity was too great, or outcome data reported were too variable or too limited to allow data to be pooled in meta-analysis. Descriptive statistics were used to summarise adverse events and device explants.

We assessed the certainty of the evidence for the comparisons and outcomes included in meta-analysis using the GRADE framework (high, moderate, low or very low certainty of evidence).[35] Magnitude of effect and certainty of the evidence were considered when drawing conclusions.

FINDINGS

The searches resulted in the identification of 1797 potentially eligible records after deduplication. Following screening of titles and abstracts, 50 records were retrieved for assessment of the full-text publication. After review of the full-text publications, 29 reports of 17 unique studies (1823 participants) were included in the review. Citations and reasons why studies were excluded on review of the full-text publication are listed in Supplement 3. The PRISMA flow diagram detailing the study selection process is presented in Figure 1.

The characteristics of the included RCTs are summarised in Supplement 4, Table S1. Twelve of the included RCTs received industry funding,[5-11 28 36 37 39 40] while 5 RCTs did not receive or declare industry funding or sponsorship.[4 12 13 29 41] Only 1 RCT funded by industry was a single centre study,[5] with 3 out of 5 the RCTs that did not receive industry funding conducted in a single centre.[4 12 13] Seven RCTs were conducted in the United States,[5 7-11 39] 9 in countries other than the United States (hereafter referred to as rest of the world [RoW])[4 6 12 13 28 29 36 40 41] and 1 in the United States and RoW.[37] All non-industry funded studies took place outside the United States.

In the included RCTs, LF-SCS as the intervention of interest or comparator was evaluated versus CMM,[6 28 36 37] dorsal root ganglion stimulation (DRGS),[39] differential target multiplexed (DTM) SCS,[9] HF-SCS,[10 12] closed-loop SCS,[8] reoperation,[5] subcutaneous stimulation in addition to SCS,[40] and physical therapy.[4] Two RCTs compared HF-SCS to CMM.[7 11] One three-armed RCT compared HF-SCS, LF-SCS and CMM,[13] 1 RCT evaluated SCS with or without a trial period,[29] and 1 RCT compared multicolumn to monocolumn programming.[41]

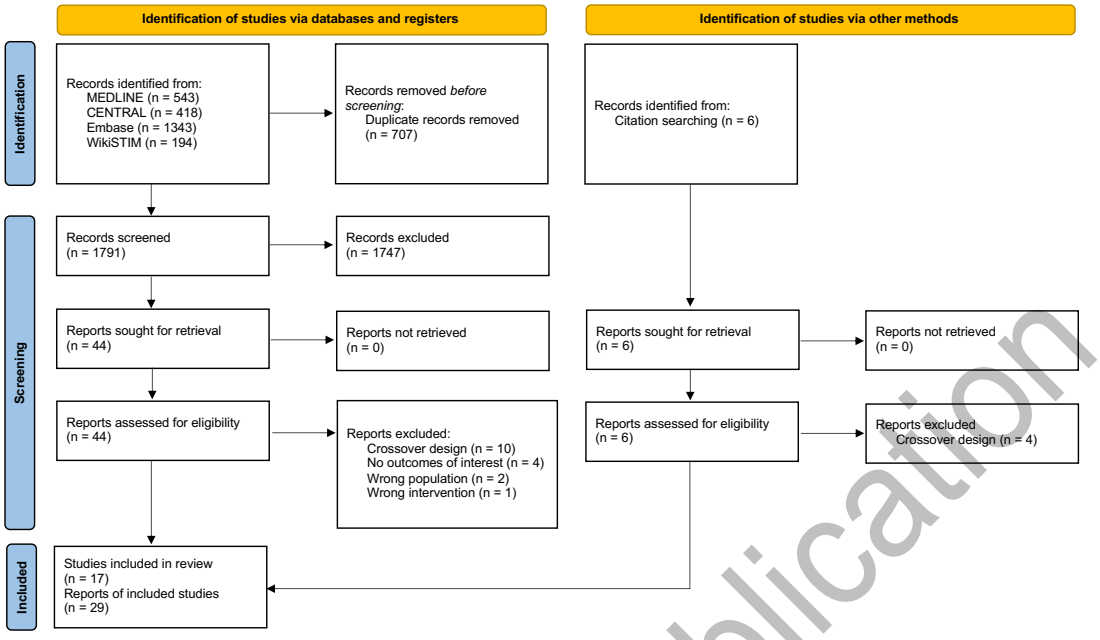

Figure 1. PRISMA 2020 flow diagram

Risk of Bias assessment

The RoB summary table is presented in Supplement 5, Table S2. One study was judged as presenting some concerns for the randomisation process domain due to some baseline imbalances observed including pathology and years since diagnosis.[13] There is often a lack of detail when describing the comparator particularly if this consists of CMM. Risk of bias due to deviations from intended interventions was not considered to be present in these instances as the population in SCS studies would already have tried several, if not all types of CMM. It is however plausible, that results of CMM in these patients would be similar to no intervention or being on a waiting list. Most studies were judged to have a high risk of bias for outcome measurement as all but one study[8] were open-label trials with outcome assessors aware of the interventions received. For participant-reported outcomes, the outcome assessor is the study participant, therefore the subjective nature of the pain assessments and the plausibility that knowledge of the intervention and beliefs of beneficial effect could have influenced these outcomes. In one study,[29] patients were not blind to whether they received a screening trial, however, this knowledge was considered as unlikely to influence participant-reported outcomes. Studies were judged as presenting some concerns for the selection of the reported

results domain where no study protocol were available or not explicitly mentioned that a prespecified analysis plan was followed. One study was judged as having some concerns for the selection of the reported results domain because the primary outcome differed between the protocol and study report and because ODI was a secondary outcome but results were only presented for the 12-month follow-up and not at the end of the 6-month primary study endpoint before crossover.[41] The overall bias for 14 studies was considered to be high because at least one domain was judged to have a high risk of bias. The overall bias was judged to be some concerns for 1 study not funded by industry.[41] The overall bias for 2 studies was considered to be low, 1 study was industry funded based in the US,[8] and 1 study was not funded by industry and based in RoW.[29]

Outcomes

Pain, physical function and HRQoL outcomes are presented in Table 1 for RCTs that received industry funding and RCTs not funded by industry. Statistically significant results were more commonly observed in favour of the intervention in industry-funded studies. All industry-funded studies reported statistically significant findings for the trial primary endpoint. Of the studies not funded by industry that found no statistically significant differences for the primary outcome, 1 compared HF-SCS to LF-SCS,[12] 1 compared SCS with or without a trial period,[29] and 1 compared multicolumn to monocolumn programming.[41] One study reported statistically significant differences at 6-months[4] but these were not maintained at last follow-up of 60-months.[42] One study observed statistically significant differences between SCS (HF-SCS and LF-SCS) and CMM but no differences between HF-SCS and LF-SCS.[13]

Device explants were not observed in 5 RCTs (3 funded by industry,[5 6 28] 2 not funded by industry[12 13] / 1 USA based[5] and 4 RoW based).[6 12 13 28] Reasons for device explant were usually reported with the most common reason being due to wound infection following SCS implant. A total of 8 explants reported in 2 studies, both funded by industry were due to loss of efficacy of the SCS device.[43 44] In addition, studies have recently started to explicitly state when device explants were not observed due to loss of efficacy.[10 43 45]

Table 1. Outcomes of randomised controlled trials included in the systematic review

Author (y), follow-up	Intervention	Control	Outcomes	Key findings	Adverse events at last follow-up	Explants at last-follow-up
Industry funding received						
De Vos (2014)[28 46] 6 months	LF-SCS	CMM	Proportion of patients with ≥50% pain reduction Pain intensity (VAS) MPQ NWC-T MPQ PRI-T MPQ QoL HRQoL (EQ-5D utility) HRQoL (EQ-5D VAS) PGIC pain Satisfaction with treatment	↑ p<0.001 ↑ p<0.001 ↑ p<0.01 ↑ p<0.01 ↑ p<0.001 ↑ p<0.05 ↑ p<0.01 ↑ p<0.01 ↑ p<0.001	1 infection during the screening trial, 2 patients perceived an incomplete overlap of the paraesthesia with the painful area during the screening trial, 2 patients with pain due to the IPG and 1 patient with coagulopathy complicating the implantation procedure	No device explants reported
Deer (2017)[39] 12 months	DRGS	LF-SCS	Proportion of patients with ≥50% pain reduction BPI severity score BPI interference score BPI activity dimension of interference BPI Affective dimension of interference Satisfaction with treatment	↑ p<0.004 (-) ↑ p<0.05 ↑ p<0.05 ↑ p<0.05 (-)	SAEs were 10.5% (8/76) in the DRGS arm and 14.5% (11/76) in the SCS arm (p=0.62). 52 procedure-related AEs were reported by 35 patients (46.1%) in the DRGS arm, and 29 procedure-related AEs were reported by 20 patients (26.3%) in the SCS arm (p=0.018). 39 device-related AEs were reported by 28 patients (36.8%) in the DRGS arm, and 24 AEs were reported by 20 patients (26.3%) in the SCS arm	Device explant required for 2 patients with SCS following infection
Fishman (2021)[9] 12 months	DTM SCS	LF-SCS	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥80% LBP reduction Proportion of patients with ≥50% LP reduction Minimal or moderate disability in ODI PROMIS global health (very good or good) PGIC proportion reporting “a great deal better” Satisfaction with treatment	DTM SCS 84% / LF-SCS 51% DTM SCS 63% / LF-SCS 28% DTM SCS 80% / LF-SCS 75% DTM SCS 76% / LF-SCS 62% DTM SCS 52% / LF-SCS 46% DTM SCS 43% / LF-SCS 30% DTM SCS 62% / LF-SCS 46%	13 SAEs in the DTM SCS group and 11 in the LF-SCS group. 4 study-related AEs in the DTM SCS group and 8 in the SCS group, the most common included trial lead dislodgement and incisional pain	1 explant following implant-site infection
Kapural (2015/2016)[7 38 47] 24 months	HF-SCS	LF-SCS	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥50% LP reduction Proportion of patients with LBP remission (pain≤2.5) Proportion of patients with LP remission (pain≤2.5) Minimal or moderate disability in ODI PGIC proportion reporting “a great deal better” Satisfaction with treatment	↑ p<0.001 ↑ p=0.003 ↑ p=0.003 ↑ p=0.001 HF-SCS 65% / LF-SCS 49% HF-SCS 34% / LF-SCS 21% HF-SCS 60% / LF-SCS 40%	5% SAEs in the HF-SCS group and 7.2% in the LF-SCS group (p=0.56); AEs in 27.7% of HF-SCS patients and 33% in LF-SCS patients (p=0.44) and uncomfortable paraesthesias in 0.0% of HF-SCS patients and 11.3% of LF-SCS subjects (p<0.001). Lead migration resulting in surgical revision occurred in 3.0% of HF-SCS and 5.2% of LF-SCS (p=0.49). LoE reported for 2 (2%) patients in HF-SCS and 7 (7.2%) in LF-SCS	At 12-months, 5 (5.6%) of patients with HF-SCS and 9 (11.1%) with LF-SCS had a device explant. 1 patient with HF-SCS was explanted and then re-implanted a month later

Kapural (2022)[10] 6 months	HF-SCS	CMM	Proportion of patients with ≥50% pain reduction Proportion of patients with ≥80% pain reduction Percentage reduction in VAS back pain Proportion of patients with MCID ≥10 in ODI Change in HRQoL (EQ-5D utility) PGIC proportion reporting "better or a great deal better"	↑ p<0.001 HF-SCS 58.5% / CMM 0% ↑ p<0.001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001	At 12-months there were 5 SAEs (2 implant site infections, 1 poor wound healing, 1 lethargy, 1 osteomyelitis). 41 AEs in 35 patients (24.1%), including 36 (87.8%) of 41 AEs that were either mild or moderate in severity. The most common AE was implant site pain (7 patients [4.8%]; 3 [2%] required IPG repositioning. Implant site infection was reported by 5 patients (3.4%), and 3 patients (2%) had transient CSF leakage. Five patients (3.4%) underwent lead revisions, 3 due to lead dislodgment and 2 due to lack of therapeutic effect	At 12-months there were 2 explants due to infections both of whom underwent reimplantation at a later date; no explants reported due to LoE
Kumar (2007)[6 48 49] 6 months	LF-SCS	CMM	Proportion of patients with ≥50% LP reduction Proportion of patients with ≥80% LP reduction Reduction in LBP Reduction in LP Improvement in ODI HRQoL (EQ-5D utility) Satisfaction with treatment	↑ p<0.001 (-) ↑ p=0.008 ↑ p<0.0001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001	At 24 months 19 patients (45%) experienced a total of 34 SCS-related complications. The most frequents were electrode migration (14%), loss of paraesthesia (12%), pain at the IPG site (12%) and infection or wound breakdown (10%). 5 patients (12%) with LoE, lost or unpleasant paraesthesia. For 13 patients (31%) surgical revision was required	No device explants reported
Mekhail (2020/2022)[8 43] 24 months	CL-SCS	OL-SCS	Proportion of patients with ≥50% overall pain reduction Proportion of patients with ≥80% overall pain reduction Percentage reduction in overall pain Improvement in ODI HRQoL (EQ-5D utility) HRQoL (EQ-5D VAS) HRQoL (SF-36 PCS) PGIC very much or much improvement	↑ p=0.001 ↑ p=0.047 ↑ p=0.01 (-) (-) (-) CL-SCS ↑ / OL-SCS ↑ CL-SCS 84% / OL-SCS 81%	4 SAEs in 4 patients (3.0%), 2 in each group were wound infection (2 [1.5%]), epidural abscess (1 [0.7%]), and lead breakage/fracture (1 [0.7%]). 42 study related AEs in 28 patients (20.9%) 28 in CL-SCS group and 14 in OL-SCS group. Most frequently reported AEs were IPG pocket pain (10 AEs, 6.7% patients) and lead migration (10 AEs, 6.7% patients)	2 (3%) explants due to LoE in the OL-SCS group and 3 (4.5%) explants due to procedure-related infections (2 [3%] in CL-SCS and 1 [1.5%] in OL-SCS); no explants reported due to LoE in the CL-SCS group
North (2005)[5] 6 months	LF-SCS	Reoperation	Proportion of patients with ≥50% pain reduction Improvement in function Satisfaction with treatment	↑ p<0.01 (-) ↑ p<0.01	1 patient had an infection at the IPG site with the system being replaced, 3 patients had hardware revisions because of electrode migration or malposition	No device explants reported
Petersen (2021)[11 45] 6 months	HF-SCS	CMM	Composite of 50% pain reduction and no deterioration on neurological examination Proportion of patients with ≥50% pain reduction Pain intensity (VAS) Proportion of patients with VAS ≤3 for 6 consecutive months HRQoL (EQ-5D utility) HRQoL (EQ-5D VAS)	↑ p<0.001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001	At 12-months, 2 treatment related SAEs (device extrusion and wound infection) and 18 AEs in 14 HF-SCS patients. At 6 months, the most frequent AEs were infection (n=3) and wound dehiscence (n=2) while a paraesthesia related adverse event was reported by 1 patient. At 12 months follow-up there were 8 procedure-related infections (3 resolved with conservative management), 2 participants had the location of the IPG revised, and 1 participant experienced lead migration that required a revision procedure	Device explant was required for 5 patients following infection with 1 patient later reimplanted; no explants reported due to LoE
Rigoard (2019)[37] 6 months	LF-SCS	CMM	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥50% LP reduction Reduction in LBP Reduction in LP Improvement in ODI HRQoL (SF-36 PCS)	↑ p=0.036 ↑ p<0.0001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001 ↑ p<0.001	At 24 months there were 24 SAEs and 63 AEs in 44 patients. The most common SAEs and AEs were implant site infection, device stimulation issue and implant site pain. The infection rate was 5%. 2 patients reported the therapeutic device as being ineffective	1 device explant in a patient that had an extradural abscess and also experienced hematoma and monoparesis

Slangen (2014)[36 44] 6 months	LF-SCS	CMM	Proportion of patients with ≥50% pain reduction (day) Proportion of patients with ≥50% pain reduction (night) Pain intensity during the day (NRS) Pain intensity during the night (NRS) HRQoL (EQ-5D utility) HRQoL (EQ-5D VAS) PGIC pain PGIC sleep Treatment success *	↑ p<0.001 ↑ p<0.01 ↑ p<0.001 ↑ p<0.003 (-) (-) ↑ p<0.001 ↑ p<0.05 ↑ p<0.01	1 patient developed PDPH following a dural puncture complicated by a lethal subdural hematoma 3 days after the procedure. During the 5 years follow-up, 10 patients reported pain in the IPG pocket, 1 patient experienced discomfort due to the battery for a long period, 4 leads were damaged and replaced and another 5 leads were repositioned to optimize paraesthesia coverage	2 patients required device explant due to an infection after implantation of the SCS system. 6 explants due to LoE
van Gorp (2016)[40 50] 3 months	SubQs+LF-SCS	LF-SCS	Proportion of patients with ≥50% LBP reduction Proportion of patients with ≥50% LP reduction Pain intensity (VAS) back Pain intensity (VAS) leg HRQoL (EQ-5D utility) HRQoL (SF-36 PCS) Improvement in ODI PGIC	↑ p=0.001 (-) ↑ p<0.001 (-) ↑ p=0.015 (-) (-) ↑ p=0.036	At 12-months there were 37 AEs in 28 patients out of 65 randomised. Most frequent AEs were pain at the location of IPG implantation (9.2%) and electrode migration in the epidural space (6.2%) and in the subcutaneous tissue (6.2%). 12 (18.5%) patients required surgery to resolve their AEs and 5 patients (7.7%) of this group of 12 were operated because of two different AEs. 4 IPGs were replaced due to high energy consumption and early battery depletion	2 patients required device explant
No industry funding received or declared						
Canós-Verdecho (2021)[13] 12 months	HF-SCS	LF-SCS, CMM	Pain intensity (NRS) Improvement in ODI Absolute improvement in pain Relative improvement in pain (%) Absolute improvement in DN4 Relative improvement in DN4 (%)	(-) p=0.257 (-) p=0.089 ↑ p=0.019 (-) p=0.097 (-) p=0.265 (-) p=0.548	5 patients with LF-SCS complained of perceiving discomfort paraesthesias with postural changes. 1 patient with HF-SCS presented occipital headache three months after implantation and 1 LF-SCS patient presented generator discomfort	No device explants reported
De Andrés (2017)[12] 12 months	HF-SCS	LF-SCS	Reduction in pain Improvement in ODI PGIC CGI improvement	(-) (-) (-) (-)	4 HF-SCS patients with lead migration from trial to permanent implant, 1 10kHz patient and 2 LF-SCS patients had lead migration with replacement at 12 months	No device explants reported
Eldabe (2020/2022)[29 51] 36 months	No screening trial**	Screening trial**	Proportion of patients with ≥50% pain reduction Proportion of patients with ≥30% pain reduction HRQoL (EQ-5D utility) HRQoL (EQ-5D VAS) Improvement in ODI (6 months) PGIC (6 months)	(-) (-) (-) (-) (-) (-)	14 AEs in the trial group and 12 AEs in the no trial group. The most common AEs were superficial wound infection and pain around the IPG site	3 explants in the trial group (2 due to wound infection and 1 due to device not switching on [patient rescheduled for implant]) and 1 explant in the no trial group due to pain at the IPG site
Kemler (2000/2008)[4 42 52] 60 months	LF-SCS	PT	Pain intensity (VAS) Proportion of patients with ≥50% pain reduction Proportion of patients with ≥30% pain reduction HRQoL Proportion of patients much improved in GPE	(-) p=0.25 LF-SCS 23% (7/31) / PT NR LF-SCS 29% (9/31) / PT NR (-) p=0.80 (-) p=0.24	29 complications occurred during 5 years of treatment, 21 (72%) took place in the first 2 years. 10 (42%) of 24 patients underwent reoperation as a result of 29 complications. IPGs were replaced 4 times in 1 patient, 2 times in another, and once in 11 patients	2 explants due to recurrent rejection or relapsing ulcerative colitis ascribed to the system. 1 explant due to infection, patient received a replacement IPG

Rigoard (2021)[41] 6 months	Multicolumn	Monocolumn	Back pain intensity (VAS) Leg pain intensity (VAS) Back pain ≥50% pain reduction Leg pain ≥50% pain reduction HRQoL (EQ-5D utility) HRQoL (EQ-5D VAS)	(-) p=0.3 (-) p=0.3 (-) p=0.5 (-) p=0.4 (-) p=0.8 (-) p=0.2	65 AEs were reported during the 12-months of the study. Most common were postoperative pain at the site of lead/IPG implantation (22.2%; 24/108 patients), while the rate of device-related infection was 10.2% (11/108 patients implanted with a multicolumn lead	6 explants due to infection

AE=adverse event; CGI=clinical global impression; CL-SCS=closed-loop spinal cord stimulation; CMM=conventional medical management; DRGS=dorsal root ganglion stimulation; DTM=differential target multiplexed; GPE=global perceived effect; HRQoL=health-related quality of life; IPG=implantable pulse generator; LoE=loss of efficacy; LP=leg pain; MCID=minimal clinical important difference; MPQ=McGill Pain Questionnaire; NR=not reported; NRS=numeric rating scale; NWC-T=total number of words chosen; ODI=Oswestry Disability Index; OL-SCS=open-loop spinal cord stimulation; PCS=Physical Component Score; PDPH=postdural puncture headache; PGIC=patient global impression of change; PRI-T=total pain rating index of words chosen; SAE=serious adverse event; SubQs=subcutaneous stimulation; VAS=visual analogue scale

* Treatment success defined as ≥50% reduction in pain intensity during daytime or night-time, or an improvement for pain and sleep of ≥6 in the score of the PGIC scale

(-) no statistically significant differences between groups

↑ statistically significant between groups in favour of intervention group

Meta-analysis: comparison of SCS versus UC

A summary of meta-analysis results for SCS versus UC is presented in Table S3.

How does industry funding affect findings of RCTs of SCS?

For all outcomes at all timepoints, results of meta-analysis showed statistically significantly greater improvements for SCS when compared to UC. Figure 2 shows the results of meta-analysis of pain intensity, change in pain intensity from baseline and ODI. The confidence intervals for subgroups (no funding or funding not disclosed, industry funding, non-industry funding) overlapped between the subgroups and no statistically significant differences between subgroups were observed. Substantial heterogeneity was observed in the subgroup meta-analysis of industry studies for pain outcomes, which may originate from differences in study findings by study location (see next section).

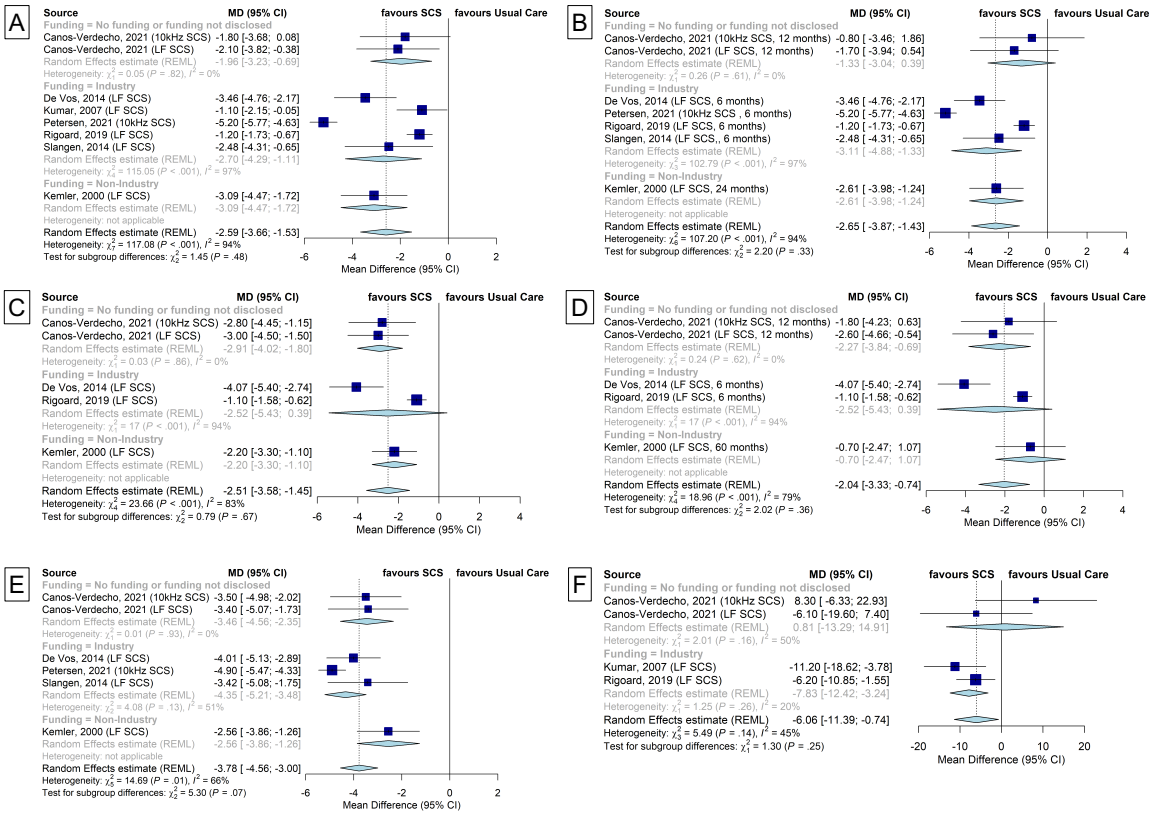

Figure 2. Meta-analysis comparing SCS with usual care based on whether funding from industry was received or not

A. Pain intensity at 6-months (680 participants); B. Pain intensity at last follow-up (583 participants); C. Change in pain intensity at 6-months (373 participants); D. Change in pain intensity at last follow-up (370 participants); E. Pain intensity at 3-months (371 participants); F. ODI at 6-months (353 participants)

How does study location affect findings of RCTs of SCS?

Tests of subgroup differences showed statistically significant differences for pain-related outcomes when considering study location (USA, RoW, USA and RoW) in subgroup meta-analysis (Figure 3). One study conducted in the USA was included in meta-analysis which compared HF-SCS to UC and reported greater differences in pain outcomes.[11] For example, the difference between HF-SCS and UC in pain intensity at 6-months in the study conducted in the USA (MD -5.20, 95% CI -5.77 to -4.63)[11] was statistically significant when compared to the studies conducted in RoW (pooled MD -2.32, 95% CI -3.16 to -1.49) and conducted in sites in the USA and RoW (MD -1.20, 95% CI -1.73 to -0.67).[37] No statistically differences between subgroups by study location were observed for ODI or EQ-5D index scores.

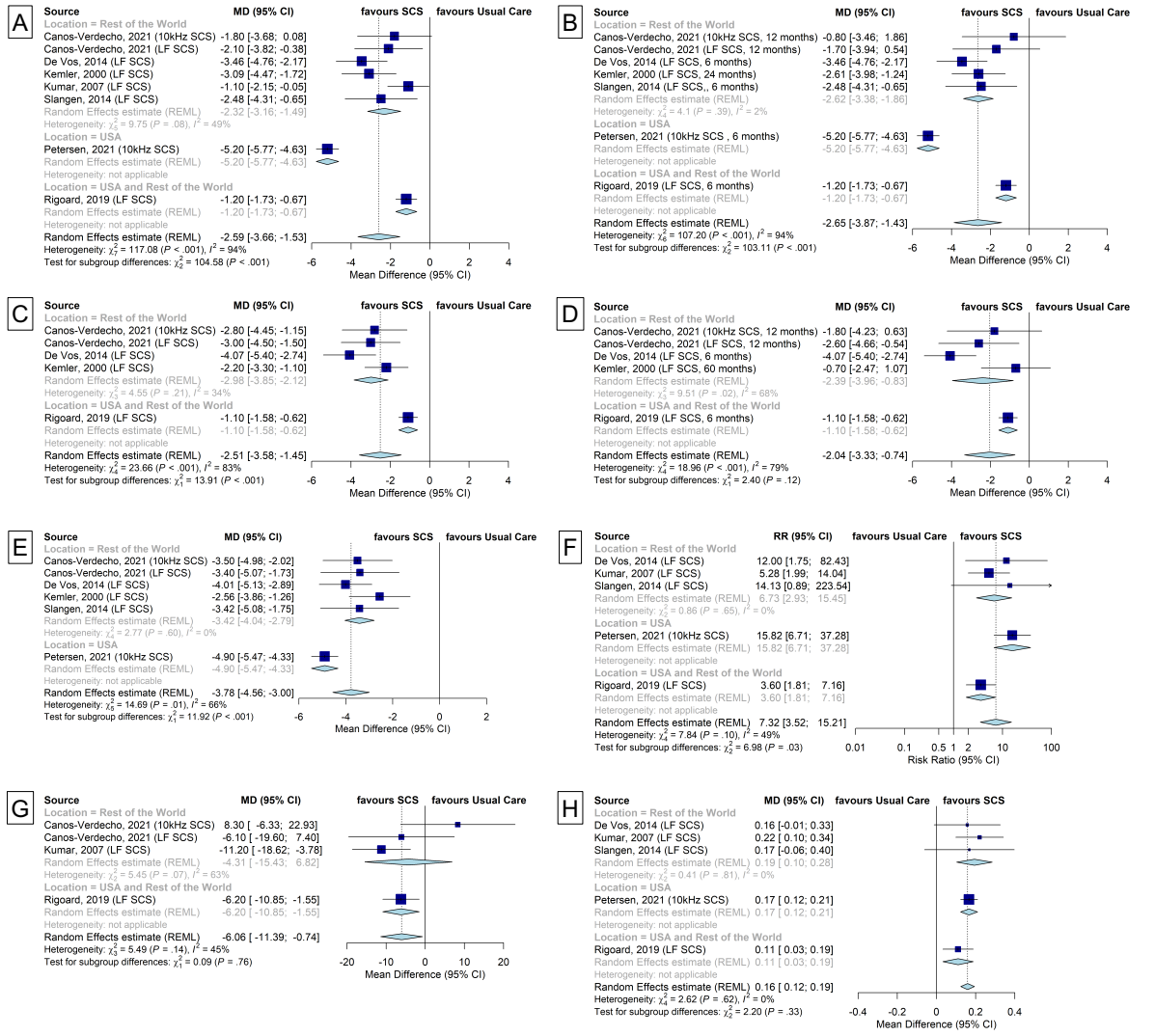

Figure 3. Meta-analysis comparing SCS with usual care based on study location

A. Pain intensity at 6-months (680 participants); B. Pain intensity at last follow-up (583 participants); C. Change in pain intensity at 6-months (373 participants); D. Change in pain intensity at last follow-up (370 participants); E. Pain intensity at 3-months (371 participants); F. Proportion of patients with 50% pain reduction (585 participants); G. ODI at 6-months (353 participants); H. EQ-5D index at 6-months (567 participants)

Meta-analysis: Comparison of HF-SCS versus LF-SCS

A summary of meta-analysis results for SCS versus UC is presented in Table S4.

Meta-analysis results for comparison of HF-SCS with LF-SCS grouped by industry funding and by location are the same since the industry-funded study was based in the USA[7] and the two studies not funded by industry were based in RoW.[12 13] For all outcomes at all timepoints, results of meta-analysis showed no differences between HF-SCS and LF-SCS. Figure 4 shows the results of meta-analysis of pain intensity, change in pain intensity from baseline and ODI. Tests of subgroup differences suggested a difference between the study with industry funding conducted in the USA and the studies with no funding conducted in RoW for pain intensity at 6-months (p=.007), 12-months (p=.001), last follow-up (p<.001) and change in pain intensity at last follow-up (p<.001), where studies with industry funding showed statistically significant advantages for HF-SCS compared to LF-SCS while studies with no funding showed no differences between HF-SCS and LF-SCS. However, only one and two studies respectively were included in the subgroups of industry funding and no funding.

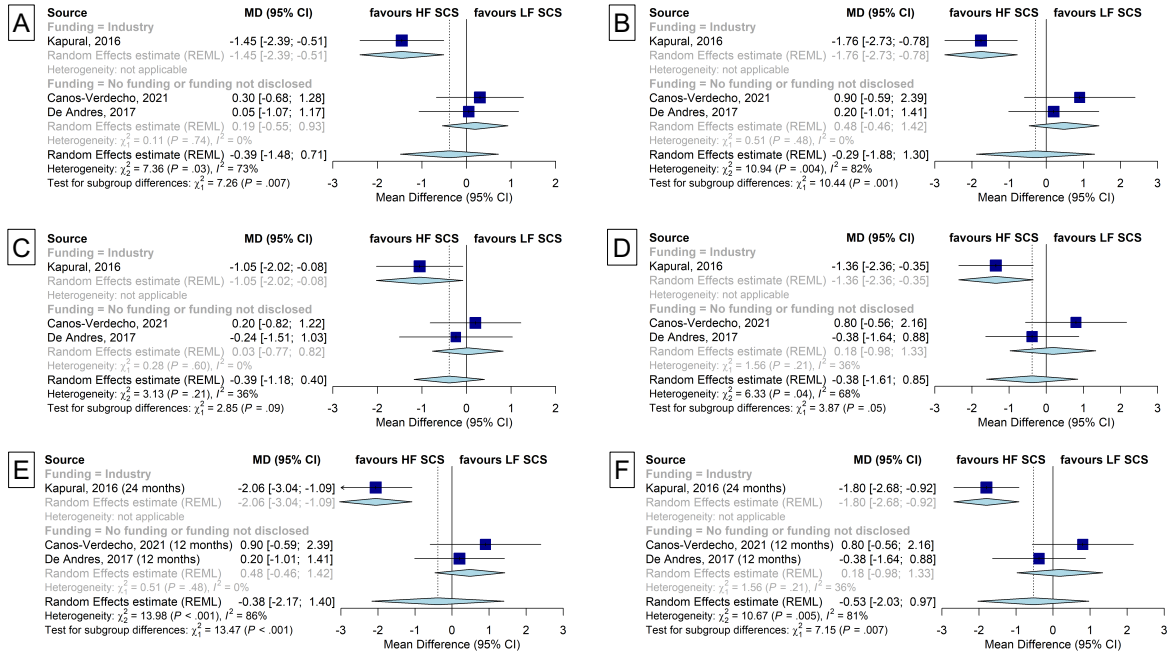

Figure 4. Meta-analysis comparing HF-SCS with LF-SCS based on whether funding from industry was received or not

A. Pain intensity at 6-months (245 participants); B. Pain intensity at 12-months (243 participants); C. Change in pain intensity at 6-months (245 participants); D. Change in pain intensity at 12-months (243 participants); E. Pain intensity at last follow-up (230 participants); F. Change in pain intensity at last follow-up (230 participants)

Sensitivity analysis including leg pain scores and meta-analysis results by pain diagnosis are presented in Supplement 6 (Figures S1 to S5). Meta-analysis could not be performed for comparisons of SCS to other interventions (e.g., other types of stimulation, surgery), and

comparisons of different modalities of SCS (e.g., closed-loop compared to open-loop SCS, SCS with or without a trial period, multicolumn compared with monocolumn).

Certainty of evidence (GRADE)

For the meta-analyses of pain, function and HRQoL outcomes, we consider that moderate certainty evidence is provided for the comparison of SCS versus UC (downgrade to the certainty of the evidence due to RoB in the measurement of the outcome in all studies) and low certainty evidence is provided for the comparison of HF-SCS versus LF-SCS (downgrades to the certainty of the evidence due to RoB in the measurement of the outcome in all studies and due to limited subgroup data available with one USA-based industry funded study and two studies without funding conducted in RoW included in meta-analysis).

Substantial heterogeneity was observed for meta-analysis of pain outcomes in industry-funded studies of SCS versus UC, which may be explained by differences in the findings of studies conducted in the USA compared to studies conducted in RoW, therefore no downgrade the certainty of evidence was made due to heterogeneity.

Data for comparisons and outcomes assessed by narrative synthesis were very limited and heterogeneous. The effect of SCS on these outcomes is very uncertain.

DISCUSSION

The results of our meta-analysis show improved outcomes for patients with SCS compared to patients with UC. Improvements of at least one minimal clinical important difference (MCID) in pain, defined as a reduction ≥2 points on the NRS,[53] were observed for the comparison of SCS with UC at 6-months (pooled MD -2.51, 95% CI -3.58 to -1.45) and last follow-up (pooled MD -2.04, 95% CI -3.33 to -0.74). No differences were observed for comparisons between HF-SCS and LF-SCS. While the differences between industry and non-industry funded studies were not statistically significant for all outcomes for comparisons of SCS with UC, statistically significant differences were observed for comparisons of HF-SCS with LF-SCS for pain intensity at 6-months, 12-months, last follow-up and change in pain intensity at last follow-up, however, only a limited number of studies could be included in the analysis. We are unable to explain this difference based on RoB assessment since all studies[12 13 38] included in this comparison were judged to have high RoB. The potential for an industry bias cannot be excluded. A Cochrane systematic review of RCTs of SCS compared with placebo (sham) stimulation observed that the evidence base is dominated by industry-sponsored studies and a high rate of conflicts of interest.[23] The authors suggested the existence of an industry bias

that cannot be explained by standard RoB assessments. It has been observed that sponsorship by industry may lead to more favourable efficacy results and conclusions than sponsorship by other sources.[15-17] It should be noted that studies independent from industry showed that SCS resulted in clinically significant improvements in outcomes when compared to baseline,[4 12 13 29 41] although not of the same magnitude as observed in studies funded by industry.

Author's relationships with SCS industry have also been raised as a concern and a possible reason to explain potential differences in results from industry and those independent from industry.[54] These suggestions were made based on the Cochrane review findings which only included comparisons of SCS with placebo (sham) where the evidence base is limited to small crossover studies.[23] The results of the Cochrane review were similar to those reported in an earlier systematic review.[22] Analysis by report of conflicts of interest would provide the same results as analysis by industry since at least some of the authors in all the studies that were funded by industry reported conflicts of interest, and the authors of studies not funded by industry included in meta-analysis did not report conflicts of interest. There are several reports of negative findings by authors with relationships with industry.[55 56] An author relationship with industry does not equate to lack of research ethics or not prioritising the best interest of their patients. We agree that results from SCS industry sponsored studies are not often observed in routine clinical practice and there is a need to improve the reporting of SCS trials.[20 57] The overall bias for all studies included in meta-analysis was considered to be high. The need to improve the design and reporting of trials applies not only to industry funded studies but also to independent studies.[57 58] The recent crossover RCT independent from industry by Hara et al,[59] reported no difference between a type of burst-SCS and placebo stimulation. Although this study did not meet the eligibility criteria for inclusion in this review, in addition to the fact that the authors evaluated an experimental mode of SCS there are several methodological issues with the study that cast doubt on its findings.[60 61]

Recent systematic reviews assessed the efficacy of SCS when compared to a placebo/sham control.[22 23 62] The two Cochrane reviews suggest that SCS is of limited value.[23 62] However, these reviews fail to mention that most of the crossover RCTs evaluated experimental modes of SCS that are not used in clinical practice. As such, those reviews are of limited value to inform patients, clinicals and policy makers since the results observed do not reflect the types of SCS used in clinical practice.[63]

The selective eligibility criteria commonly used in RCTs although essential for internal validity, may lead to impaired generalisability of results to other patient populations.[64] As psychosocial factors, patients expectations and healthcare economics vary from one country to another, study location may also have implications to generalisability to other settings, patient

populations and may require further exploration.[65] Although the SCS procedure including use of screening trials prior to full implantation of the device and implanting techniques are fairly standardised across countries,[29 55] the generalisability of RCT results from one country to another is not often considered, while this could be of major interest.[66]

Significant differences for the comparison of SCS versus UC were observed for pain intensity outcomes when considering study location, with studies conducted in the USA reporting greater improvements with SCS than studies conducted in RoW. The results of the meta-analysis by study location need to be interpreted with caution because only one of the studies included in meta-analysis was conducted in the USA and compared HF-SCS with UC.[11] However, this study reported significantly greater improvements for the SCS arm than the other studies included. It is interesting to note that differences when considering study location were only significant for pain related outcomes and no significant differences were observed for EQ-5D index. Outcomes beyond pain intensity alone should be explored to evaluate patient response to SCS.[67]

Strengths and limitations

As previously acknowledged in several publications there is a lack of RCTs of SCS not funded by industry. A RoB assessment was conducted for all included RCTs and all the findings presented. Five non-industry funded studies were identified in this systematic review, of which only three could be included in the meta-analysis. Only a very limited number of studies were available for the comparison of HF-SCS with LF-SCS. The use of different comparators in the included RCTs limits the number of studies that could be included in meta-analysis. Several comparisons were based on small sample sizes and subgroup analysis could be affected by other covariates. Several outcomes had high levels of heterogeneity despite subgroup analysis. Due to a small number of studies included in each meta-analysis, and each subgroup within each meta-analysis, we were not able to reliably assess the presence of publication bias and therefore cannot rule out the presence of publication bias in the meta-analyses.

CONCLUSIONS

Our findings suggest that the perceived impact of industry funding in findings of SCS studies may be overstated. SCS provides better outcomes than UC and the results do not differ significantly between studies funded by industry and those independent from industry. Industry funding seems to have played a part in comparisons between HF-SCS and LF-SCS. Meta-analysis results showed no significant differences between HF-SCS and LF-SCS but

significant differences for subgroup meta-analysis based on industry funding for pain-related outcomes but no difference for quality of life.

Contributors: SE and RVD conceptualised and designed the study. SE, SN, SC and RVD co-wrote the protocol. MM developed the literature search strategies and conducted the searches. RVD, SC and SE performed the study selection. SC, RVD and SN extracted the data. SC, MM and RVD conducted the risk of bias assessment. SN performed the data analysis. The results were summarised by RVD and SN and interpreted in collaboration with all authors. SE, SN, SC and RVD drafted the manuscript. SE, SN, SC, MM, LG, SH, NM, MM, PR and RVD critically revised the manuscript for important intellectual content and approved the final version of the manuscript. All authors had full access to all data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. SE and RVD are the guarantors who accepts full responsibility for the finished work and the conduct of the study as well as having access to the data and controlled the decision to publish.

REFERENCES

1. National Institute for Health and Care Excellence (NICE). Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. Technology appraisal guidance [TA159] 2008 [Available from: https://www.nice.org.uk/guidance/ta159. Accessed 31st October 2022.
2. Medical Advisory Secretariat. Spinal cord stimulation for neuropathic pain: an evidence-based analysis. *Ont Health Technol Assess Ser* 2005;5(4):1-78. [published Online First: 2005/01/01]
3. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth Analg* 1967;46(4):489-91. [published Online First: 1967/07/01]
4. Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;343(9):618-24. doi: 10.1056/nejm200008313430904 [published Online First: 2000/08/31]
5. North RB, Kidd DH, Farrokhi F, et al. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery* 2005;56(1):98-106; discussion 06-7. doi: 10.1227/01.neu.0000144839.65524.e0 [published Online First: 2004/12/25]
6. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;132(1-2):179-88. doi: 10.1016/j.pain.2007.07.028 [published Online First: 2007/09/12]
7. Kapural L, Yu C, Doust MW, et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. *Anesthesiology* 2015;123(4):851-60. doi: 10.1097/aln.0000000000000774
8. Mekhail N, Levy RM, Deer TR, et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *The Lancet Neurology* 2020;19(2):123-34. doi: 10.1016/S1474-4422(19)30414-4
9. Fishman M, Cordner H, Justiz R, et al. Twelve-Month results from multicenter, open-label, randomized controlled clinical trial comparing differential target multiplexed spinal cord stimulation and traditional spinal cord stimulation in subjects with chronic intractable back pain and leg pain. *Pain Pract* 2021;21(8):912-23. doi: 10.1111/papr.13066 [published Online First: 2021/08/08]
10. Kapural L, Jameson J, Johnson C, et al. Treatment of nonsurgical refractory back pain with high-frequency spinal cord stimulation at 10 kHz: 12-month results of a pragmatic, multicenter, randomized controlled trial. *J Neurosurg Spine* 2022:1-12. doi: 10.3171/2021.12.Spine211301 [published Online First: 2022/02/12]
11. Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial. *JAMA Neurol* 2021;78(6):687-98. doi: 10.1001/jamaneurol.2021.0538 [published Online First: 2021/04/06]
12. De Andres J, Monsalve-Dolz V, Fabregat-Cid G, et al. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. *Pain Med* 2017;18(12):2401-21. doi: 10.1093/pm/pnx241 [published Online First: 2017/11/11]
13. Canós-Verdecho A, Abejón D, Robledo R, et al. Randomized Prospective Study in Patients With Complex Regional Pain Syndrome of the Upper Limb With High-Frequency Spinal Cord Stimulation (10-kHz) and Low-Frequency Spinal Cord Stimulation. *Neuromodulation* 2021;24(3):448-58. doi: 10.1111/ner.13358 [published Online First: 2021/01/20]
14. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869. doi: 10.1136/bmj.c869
15. Lundh A, Lexchin J, Mintzes B, et al. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017(2) doi: 10.1002/14651858.MR000033.pub3
16. Lexchin J, Bero LA, Djulbegovic B, et al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326(7400):1167-70. doi: 10.1136/bmj.326.7400.1167
17. Sismondo S. Pharmaceutical company funding and its consequences: a qualitative systematic review. *Contemp Clin Trials* 2008;29(2):109-13. doi: 10.1016/j.cct.2007.08.001 [published Online First: 2007/10/09]

18. Hussain N, Brull R, Sheehy B, et al. Perineural Liposomal Bupivacaine Is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia. *Anesthesiology* 2021;134(2):147-64. doi: 10.1097/aln.0000000000003651 [published Online First: 2020/12/30]
19. Bhandari M, Jönsson A, Bühren V. Conducting industry-partnered trials in orthopaedic surgery. *Injury* 2006;37(4):361-6. doi: 10.1016/j.injury.2006.01.029 [published Online First: 2006/02/14]
20. Duarte RV, McNicol E, Colloca L, et al. Randomized Placebo-/Sham-Controlled Trials of Spinal Cord Stimulation: A Systematic Review and Methodological Appraisal. *Neuromodulation* 2020;23(1):10-18. doi: 10.1111/ner.13018 [published Online First: 2019/07/16]
21. McNicol E, Ferguson M, Bungay K, et al. Systematic Review of Research Methods and Reporting Quality of Randomized Clinical Trials of Spinal Cord Stimulation for Pain. *J Pain* 2021;22(2):127-42. doi: 10.1016/j.jpain.2020.05.001 [published Online First: 2020/06/24]
22. Duarte RV, Nevitt S, McNicol E, et al. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. *Pain* 2020;161(1):24-35. doi: 10.1097/j.pain.0000000000001689 [published Online First: 2019/08/28]
23. O'Connell NE, Ferraro MC, Gibson W, et al. Implanted spinal neuromodulation interventions for chronic pain in adults. *Cochrane Database Syst Rev* 2021;12(12):Cd013756. doi: 10.1002/14651858.CD013756.pub2 [published Online First: 2021/12/03]
24. Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. *Lancet* 2021;397(10289):2111-24. doi: 10.1016/s0140-6736(21)00794-7 [published Online First: 2021/06/02]
25. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;372:n160. doi: 10.1136/bmj.n160
26. Lefebvre C, Glanville J, Briscoe S, et al. Chapter 4: Searching for and selecting studies. In: Higgins J, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions version 63 (updated February 2022). Available from www.training.cochrane.org/handbook.: Cochrane 2022.
27. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj* 2019;366:l4898. doi: 10.1136/bmj.l4898 [published Online First: 2019/08/30]
28. de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain* 2014;155(11):2426-31. doi: 10.1016/j.pain.2014.08.031
29. Eldabe S, Duarte RV, Gulve A, et al. Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility and cost-effectiveness (TRIAL-STIM)? A randomised controlled trial. *Pain* 2020;161(12):2820-29. doi: 10.1097/j.pain.0000000000001977 [published Online First: 2020/07/04]
30. Duarte RV, Nevitt S, Maden M, et al. Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data. *Pain* 2021;162(11):2635-43. doi: 10.1097/j.pain.0000000000002262 [published Online First: 2021/04/20]
31. Higgins J, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins J, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions version 63 (updated February 2022). Available from www.training.cochrane.org/handbook.: Cochrane 2022.
32. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019;22(4):153-60. doi: 10.1136/ebmental-2019-300117 [published Online First: 2019/09/30]
33. Langan D, Higgins JPT, Jackson D, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods* 2019;10(1):83-98. doi: 10.1002/jrsm.1316 [published Online First: 2018/08/02]
34. Deeks J, Higgins J, Altman D. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins J, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions v63 (updated February 2022): Cochrane 2022:241-84.
35. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]
36. Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. *Diabetes care* 2014;37(11):3016-24. doi: https://dx.doi.org/10.2337/dc14-0684

37. Rigoard P, Basu S, Desai M, et al. Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial. *Pain* 2019;160(6):1410-20. doi: 10.1097/j.pain.0000000000001510 [published Online First: 2019/02/06]
38. Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. *Neurosurgery* 2016;79(5):667-77. doi: 10.1227/NEU.0000000000001418
39. Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *PAIN* 2017;158(4):669-81. doi: 10.1097/j.pain.0000000000000814
40. van Gorp EJ, Teernstra OP, Gültuna I, et al. Subcutaneous Stimulation as ADD-ON Therapy to Spinal Cord Stimulation Is Effective in Treating Low Back Pain in Patients With Failed Back Surgery Syndrome: A Multicenter Randomized Controlled Trial. *Neuromodulation* 2016;19(2):171-8. doi: 10.1111/ner.12385 [published Online First: 2016/02/20]
41. Rigoard P, Billot M, Ingrand P, et al. How Should we Use Multicolumn Spinal Cord Stimulation to Optimize Back Pain Spatial Neural Targeting? A Prospective, Multicenter, Randomized, Double-Blind, Controlled Trial (ESTIMET Study). *Neuromodulation* 2021;24(1):86-101. doi: 10.1111/ner.13251 [published Online First: 2020/09/01]
42. Kemler MA, de Vet HC, Barendse GA, et al. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg* 2008;108(2):292-8. doi: 10.3171/jns/2008/108/2/0292 [published Online First: 2008/02/05]
43. Mekhail N, Levy RM, Deer TR, et al. Durability of Clinical and Quality-of-Life Outcomes of Closed-Loop Spinal Cord Stimulation for Chronic Back and Leg Pain: A Secondary Analysis of the Evoke Randomized Clinical Trial. *JAMA Neurology* 2022;3(79):251-160. doi: 10.1001/jamaneurol.2021.4998
44. van Beek M, Geurts JW, Slangen R, et al. Severity of Neuropathy Is Associated With Long-term Spinal Cord Stimulation Outcome in Painful Diabetic Peripheral Neuropathy: Five-Year Follow-up of a Prospective Two-Center Clinical Trial. *Diabetes care* 2018;41(1):32-38. doi: https://dx.doi.org/10.2337/dc17-0983
45. Petersen EA, Stauss TG, Scowcroft JA, et al. High-Frequency 10-kHz Spinal Cord Stimulation Improves Health-Related Quality of Life in Patients With Refractory Painful Diabetic Neuropathy: 12-Month Results From a Randomized Controlled Trial. *Mayo Clin Proc Innov Qual Outcomes* 2022;6(4):347-60. doi: 10.1016/j.mayocpiqo.2022.05.003 [published Online First: 2022/07/12]
46. Duarte RV, Andronis L, Lenders M, et al. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. *Quality of life research* 2016;25(7):1771-77. doi: 10.1007/s11136-015-1211-4
47. Food and Drug Administration. Summary of Safety and Effeciveness Data (SSED): Senza Spinal Cord Stimulation (SCS) system 2015 [Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130022B.pdf [accessed August 2022].
48. Kumar K, Taylor RS, Jacques L, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery* 2008;63(4):762-70; discussion 70. doi: 10.1227/01.Neu.0000325731.46702.D9 [published Online First: 2008/11/05]
49. Manca A, Kumar K, Taylor RS, et al. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). *Eur J Pain* 2008;12(8):1047-58. doi: 10.1016/j.ejpain.2008.01.014 [published Online First: 2008/03/25]
50. van Gorp E, Teernstra O, Aukes HJ, et al. Long-Term Effect of Peripheral Nerve Field Stimulation as Add-On Therapy to Spinal Cord Stimulation to Treat Low Back Pain in Failed Back Surgery Syndrome Patients: A 12-Month Follow-Up of a Randomized Controlled Study. *Neuromodulation* 2019;22(8):970-77. doi: 10.1111/ner.12776 [published Online First: 2018/04/03]
51. Eldabe S, Nevitt S, Griffiths S, et al. Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility (TRIAL-STIM)? 36-month results from a randomised controlled trial. *Neurosurgery* In press
52. Kemler MA, De Vet HC, Barendse GA, et al. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2004;55(1):13-8. doi: 10.1002/ana.10996 [published Online First: 2004/01/06]

53. Farrar JT, Young JP, Jr., LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94(2):149-58. doi: 10.1016/s0304-3959(01)00349-9 [published Online First: 2001/11/03]
54. Ferraro MC, Gibson W, Rice ASC, et al. Spinal cord stimulation for chronic pain. *The Lancet Neurology* 2022;21(5):405. doi: 10.1016/S1474-4422(22)00096-5
55. Eldabe S, Copley S, Gulve A, et al. A prospective long-term follow-up of dorsal root ganglion stimulation for the management of chronic intractable pain. *PAIN* 2022;163(4):702-10. doi: 10.1097/j.pain.0000000000002405
56. Eldabe S, Duarte R, Gulve A, et al. Analgesic Efficacy of "Burst" and Tonic (500 Hz) Spinal Cord Stimulation Patterns: A Randomized Placebo-Controlled Crossover Study. *Neuromodulation* 2021;24(3):471-78. doi: 10.1111/ner.13321 [published Online First: 2020/12/01]
57. Duarte RV, Bresnahan R, Copley S, et al. Reporting Guidelines for Clinical Trial Protocols and Reports of Implantable Neurostimulation Devices: Protocol for the SPIRIT-iNeurostim and CONSORT-iNeurostim Extensions. *Neuromodulation* 2022;25(7):1045-49. doi: 10.1016/j.neurom.2021.10.006
58. Katz N, Dworkin RH, North R, et al. Research design considerations for randomized controlled trials of spinal cord stimulation for pain: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials/Institute of Neuromodulation/International Neuromodulation Society recommendations. *Pain* 2021;162(7):1935-56. doi: 10.1097/j.pain.0000000000002204 [published Online First: 2021/01/21]
59. Hara S, Andresen H, Solheim O, et al. Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial. *Jama* 2022;328(15):1506-14. doi: 10.1001/jama.2022.18231 [published Online First: 2022/10/19]
60. Eldabe S, Gilligan C, Taylor RS, et al. Issues in design, conduct, and conclusions of JAMA's Hara et al.'s randomized clinical trial of spinal cord burst stimulation versus placebo stimulation on disability in patients with chronic radicular pain after lumbar spine surgery. *Pain Pract* 2023;23(3):232-33. doi: 10.1111/papr.13186 [published Online First: 2022/12/13]
61. Taylor RS, Eldabe S. Placebo (Sham) Controlled Trials of Spinal Cord Stimulation. *Neuromodulation* 2023;26(2):474-75. doi: 10.1016/j.neurom.2022.11.013
62. Traeger AC, Gilbert SE, Harris IA, et al. Spinal cord stimulation for low back pain. *Cochrane Database of Systematic Reviews* 2023;2023(3) doi: 10.1002/14651858.CD014789.pub2
63. Staats PS, Taylor RS, Gilligan C, et al. Limitations of the Cochrane review of spinal cord stimulation for low back pain. *Pain Practice* In press
64. Van Spall HG, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *Jama* 2007;297(11):1233-40. doi: 10.1001/jama.297.11.1233 [published Online First: 2007/03/22]
65. Yusuf S, Wittes J. Interpreting Geographic Variations in Results of Randomized, Controlled Trials. *N Engl J Med* 2016;375(23):2263-71. doi: 10.1056/NEJMra1510065 [published Online First: 2016/12/14]
66. North R, Desai MJ, Vangeneugden J, et al. Postoperative Infections Associated With Prolonged Spinal Cord Stimulation Trial Duration (PROMISE RCT). *Neuromodulation* 2020;23(5):620-25. doi: 10.1111/ner.13141 [published Online First: 2020/04/09]
67. Levy R, Mekhail N, Abd-Elsayed A, et al. Holistic treatment response: an international expert panel definition and criteria for a new paradigm in the assessment of clinical outcomes of spinal cord stimulation. *Neuromodulation* In press