

# **Spinal Cord Stimulators**

**Review of comparative clinical and cost-effectiveness to support the Prescribed List Post-Listing Review**

**Final Report**

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This report was prepared by Samara Lewis, Natasha Prakash, Allison Wyndham, Jenny Ring, and Sue Campbell from Health Research Consulting (hereco). The report was commissioned by the Australian Government Department of Health and Aged Care.

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# Abbreviations

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ABDR	Australian Breast Device Registry	GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ACSQHC	Australian Commission on Safety and Quality in Health Care	HAD	Hospital Anxiety and Depression scale
AE	Adverse events	HF	High-frequency
AIHW	Australian Institute of Health and Welfare	HFSCS	High Frequency Spinal Cord Stimulation
AIMD	Active implantable medical device	HRQoL	Health-related quality of life
ANZCA	Australian and New Zealand College of Anaesthetists	HTA	Health technology assessment
ANZCTR	Australian New Zealand Clinical Trials Registry	ICD	International Classification of Diseases
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry	ICER	Incremental cost-effectiveness ratio
AP	Angina pectoris	IFU	Instructions for Use
ARTG	Australian Registry of Therapeutic Goods	IHPA	Independent Hospital Pricing Authority
ASIPP	American Society of Interventional Pain Physicians	INS	International Neuromodulation Society
ASPN	American Society of Pain and Neuroscience	IPG	Implantable pulse generator
BMT	Best medical treatment	IPM	Interventional Pain Management
BPI	Brief Pain Inventory	ITT	intention to treat
CABG	Coronary artery bypass grafting	LBP	low back pain
CBLP	Chronic back and leg pain	LOS	length of stay
CEA	Cost-effectiveness analysis	MBNS	Medial branch nerve stimulator
CHEPA	Centre for Health Economics and Policy Analysis	MBS	Medicare Benefits Schedule
CHSPR	Centre for Health Services and Policy Research	MCP	multicolumn programming
CI	Confidence interval	MD	Mean difference
CLBP	Chronic low back pain	MDHTAC	Medical Devices and Human Tissue Advisory Committee
CLI	Critical limb ischaemia	MIB	Medtech innovation briefings
CLS	Closed Loop Stimulator	MM	medical management
CMM	Conventional medical management	MME	Morphine milligram equivalent
COI	Conflict of interest	MOSS	Medical Outcomes Study Sleep
CPG	Clinical practice guideline	MSAC	Medical Services Advisory Committee
CPRS	Complex regional pain syndrome	MTAA	Medical Technology Association of Australia
CUA	Cost-utility analysis	MTG	Medical technologies guidance
DASH	Disabilities of the Arm, Shoulder, and Hand Questionnaire	NA	Not applicable
DASS	Depression, Anxiety and Stress Scale	NACC	Neuromodulation Appropriateness Consensus Committee/ the Neurostimulation Appropriateness Consensus Committee
DoHAC	Department of Health and Aged Care	NICE	National Institute of Health and Care Excellence
DPN	Diabetic peripheral neuropathy	NL	The Netherlands
DRG	Dorsal root ganglion	NNTB	number needed to benefit
DRGS	Dorsal root ganglion stimulator/stimulation	NNTH	number needed to harm
DTM	differential target multiplexed	NR	not reported
EAN	European Academy of Neurology	NRS	numerical rating scale
EPT	External pulse transmitter	NS	not significant
EQ	EuroQOL	NSAID	Non-steroidal anti-inflammatory drugs
FBSS	Failed back surgery syndrome	NSANZ	Neuromodulation Society of Australia and New Zealand
FDA	Food and Drug Administration	ODI	Oswestry Disability Index
FSQ	Fibromyalgia Survey Questionnaire	OMM	optimal medical management
GMDN	Global Medical Device Nomenclature	ONS	occipital nerve stimulation

PAD	Peripheral arterial disease	RR	relative risk
PDI	General Pain Disability Index	RSD	reflex sympathetic dystrophy
PDN	Painful Diabetic Neuropathy	SAE	Serious adverse events
PDPN	painful diabetic polyneuropathy	ScHARR	School of Health and Related Research
PENS	Percutaneous Electrical Nerve Stimulation	SCS	Spinal cord stimulator/stimulation
PICO	population, intervention, comparator, outcome	SD	standard deviation
PL	Prescribed List	SEM	standard error of the mean
PLAC	Prostheses List Advisory Committee	SFMPQ	Short Form McGill Pain Questionnaire
PLR	Post-listing review	SFN	Small fibre neuropathies
PLRT	Prostheses List Reform Taskforce	SIGN	Scottish Intercollegiate Guidelines Network
PLS	Post-laminectomy syndrome	SNS	Sacral nerve stimulators
PMR	percutaneous myocardial laser revascularisation	SR	Systematic review
PNS	Peripheral nerve stimulators	TGA	Therapeutic Goods Association
PSPS	Persistent spinal pain syndrome	UC	Usual care
PT	physical therapy	UEP	Upper extremity pain
QALY	quality adjusted life year	UK	United Kingdom
QoL	quality of life	USPSTF	United States Preventive Services Task Force
RAP	Refractory angina pectoris	VAS	Visual analogue scale
RCT	Randomised controlled trial	VCOR	Victorian Cardiac Outcomes Registry
RD	risk difference	VNS	Vagal nerve stimulators
RDQ	Roland Disability Questionnaire	WHO	World Health Organisation

# Executive Summary

## Introduction

Concerns about the long-term safety and effectiveness of spinal cord stimulators (SCS) were raised following publication of a review based on analysis of Therapeutic Goods Association (TGA) adverse events (AEs) data (Jones et al. 2022). As these devices have not been assessed by the Medical Services Advisory Committee (MSAC) or the Prostheses List Advisory Committee (PLAC) (now the Medical Devices and Human Tissue Advisory Committee [MDHTAC]), the purpose of this post-listing review (PLR) is to review the comparative clinical effectiveness and cost-effectiveness of SCS to inform decisions regarding the associated listings on the Prescribed List (PL).

The findings are based on consideration of key documents supplied by the Department of Health and Aged Care (DoHAC), a pragmatic review of the published literature and targeted stakeholder consultation.

SCS devices are listed in Group 04.05.01 Pulse Generators under the ‘Neurostimulation Therapies for Pain’ Subcategory. This category includes SCS, dorsal root ganglion stimulators (DRGS), and two peripheral nerve stimulators (PNS). The PNS devices are out of scope for this review.

## Summary of findings

### Clinical effectiveness – chronic (non-ischaemic) pain

Two Cochrane systematic reviews (SRs) considering the effectiveness of SCS were recently published and provide the most recent and comprehensive summary of the available evidence. The two reviews have substantial overlap in methodology and include eight of the same studies.

Traeger (2023) compared SCS to placebo (sham stimulation) or as an addition to medical management for the treatment of low back pain. The findings by outcome and follow-up time (medium and long-term only) are summarised in Table ES 1, which includes the number of randomised controlled trials (RCTs) and participants, and the author’s assessment of the quality of the evidence using GRADE.

**Table ES 1 Summary of findings in Traeger Cochrane Review (2023) at medium and long-term follow-up**

Outcomes	No. RCTs; N	Quality of evidence	Statistical significance	Clinical importance <sup>a</sup>
<b>SCS versus placebo(sham)</b>				
<b>Pain intensity</b>				
Low back pain	1; N=50 (M)	moderate	No effect	No difference
Leg pain	1; N=50 (M)	moderate	No effect	No difference
<b>Function</b>	1; N=50 (M)	moderate	No effect	No difference
<b>HRQoL</b>	1; N=50 (M)	moderate	No effect	No difference
<b>SCS + MM versus MM alone</b>				
<b>Pain intensity</b>				
Low back pain	3; N=430 (M)	very low	No effect	Favours SCS
Leg pain	2; N=290 (M)	very low	Favours SCS	Favours SCS
≥50% better	3; N=430 (M)	very low	Favours SCS	Favours SCS
	1; N=100 (L)	very low	Favours SCS	Favours SCS
<b>Function</b>	3; N=430 (M)	low	Favours SCS	Favours SCS
<b>HRQoL</b>	2; N=289 (M)	very low	No effect	NR
<b>Harms</b>				
AEs	2; N=336 (M)	very low	Favours SCS	NR

Outcomes	No. RCTs; N	Quality of evidence	Statistical significance	Clinical importance <sup>a</sup>
SAEs	1; N=140 (M)	low	No effect	NR
<b>Secondary outcomes</b>				
Opioid use	2; N=290 (M)	low	Favours SCS	NR
Daily MMEs	3; N=430 (M)	low	No effect	NR

Source: based on data from Traeger (2023) Cochrane review

Abbreviations: AE, adverse event; HRQoL, health-related quality of life; MM, medical management; MMEs, morphine milligram equivalents; N, population; NR, not reported; RCT, randomised controlled trial; SAE, serious adverse event; SCS, spinal cord stimulation

<sup>a</sup> Clinical importance is defined by a predetermined threshold of  $\geq 10$  points for pain intensity (derived from O'Connell 2021) and function (derived from Hara 2022).

Key: orange = very low quality evidence; yellow = low quality evidence; blue = moderate quality evidence; green = favours intervention.

(M) = medium-term outcomes  $\geq 3$  months to  $< 12$  months; (L) = long-term outcomes  $\geq 12$  months.

O'Connell compared SCS to either placebo (sham) or as an addition to medical management for the treatment of chronic (non-ischaemic, non-cancer) pain. Medium or long-term follow-up was only available for the comparison to medical management. These findings are summarised in Table ES 2, which includes the number of RCTs and participants, and the author's assessment of the quality of the evidence using GRADE. No outcomes with medium-term or greater follow-up were identified for studies of SCS compared to placebo.

**Table ES 2 Summary of findings in O'Connell Cochrane Review (2021) at medium and long-term follow-up**

Outcomes	No. RCTs; N	Quality of evidence	Statistical significance	Clinical importance <sup>a</sup>
<b>SCS versus placebo (sham)</b>				
<i>no evidence at medium or long-term follow-up</i>				
<b>SCS + other intervention (MM or physical therapy) versus other intervention alone</b>				
<b>Pain intensity</b>				
Continuous outcomes (VAS 0-100)	5; N=634 (M)	low	Favours SCS	Favours SCS
<i>mean difference</i>	1; N=44 (L)	very low	No effect	No difference
Proportion with $\geq 50\%$ pain relief	5; N=597 (M)	low	Favours SCS	Favours SCS
	1; N=87 (L)	very low	Favours SCS	Favours SCS
<b>AEs</b>				
Lead failure/displacement	3; N=330 (M)	very low	No effect	NR
	1; N=44 (L)	very low	Favours MM	NR
Infection	4; N=548 (M)	low	Favours MM	NR
Reoperation/reimplantation	4; N=548 (M)	very low	Favours MM	NR
	1; N=44 (L)	very low	Favours MM	NR
Other AEs	2; N=278 (M)	low	No effect	NR
	1; N=100 (L)	very low	No effect	NR
<b>Secondary outcomes</b>				
Disability	2; N=312 (M)	very low	No effect	No difference
HRQoL	5; N=595 (M)	low	Effect in favour of SCS	NR
	1; N=44 (L)	very low	No effect	No difference
Medication use	2; N=154 (M)	low <sup>b</sup>	No effect	No difference

Source: based on data from O'Connell (2021) Cochrane review

Abbreviations: AE, adverse event; HRQoL, health-related quality of life; MM, medical management; N, population; NR, not reported; RCT, randomised controlled trial; SCS, spinal cord stimulation; VAS, visual analogue scale.

<sup>a</sup> Clinical importance is defined by a predetermined threshold of  $\geq 10$  points for pain intensity (derived from O'Connell 2021) and function (derived from Hara 2022).

<sup>b</sup> very low certainty of evidence on anticonvulsants, low for other medication types.



Key: orange = very low quality evidence; yellow = low quality evidence; blue = moderate quality evidence; green = favours intervention; pink = favours comparator.

(M) = medium-term outcomes  $\geq$  3 months to  $<$ 12 months; (L) = long-term outcomes  $\geq$  12 months.

The two Cochrane reviews conclude that SCS may not be beneficial in their respective populations. Whilst open-label comparisons to conventional medical management (CMM) demonstrated large, clinically significant effects, sham-controlled studies reported only small, possibly clinically insignificant effects; where analyses were restricted to studies that were adequately blinded, there was no evidence for a treatment effect. This is despite the high risk of bias in the sham-controlled studies including short-term duration, lack of washout periods, per-protocol analyses and lack of formal assessment of blinding success. The authors propose that the large effects in the open-label studies may be explained by contextual (placebo) effects.

A key difference between the two Cochrane reviews is the inclusion of the Hara (2022) study, which was published after the O'Connell (2021) review but is included in Traeger (2023). Hara (2022) is a cross-over RCT comparing burst SCS with placebo (sham) SCS in 50 patients with chronic radicular pain. Participants underwent two three-month periods with each condition and therefore it is the only study that provides medium-term outcomes for the placebo comparator. The study reported no significant differences between SCS and placebo for any outcomes (SCS versus placebo in Table ES 1).

Although a number of concerns have been raised regarding the conduct of this trial, the key issue is the validity of the SCS as applied in the active stimulation arm of the trial. The authors label this stimulation 'burst'; however, it differs from BurstDR™ stimulation, raising concerns that the trial was a 'placebo versus placebo' trial. The stimulation parameters tested, and the prohibition on any change to the parameters during treatment to preserve blinding (which differs to clinical practice), limits the applicability of the trial, however it remains the strongest methodological design of the included trials.

Cochrane reviews have narrow inclusion criteria and may have omitted a much larger volume of relevant evidence. Therefore, all evidence provided by sponsors and stakeholders, together with evidence excluded from the Cochrane reviews, was collated for this post-listing review (PLR) and additional RCTs and appropriately adjusted comparative observational studies were considered as supplementary evidence.

Nine additional RCTs were considered as they provided at least medium-term follow-up (three months or more) and reported a measure of pain intensity. Although small differences in pain outcomes were found for some trials, all favouring the intervention, many reported no difference. Two of the nine trials stated they were blinded, one of which reported no difference between multicolumn SCS programming and conventional SCS in patients with failed back surgery syndrome (FBSS) (ESTIMET). The second blinded RCT (EVOKE), which was in patients with chronic intractable pain of the back and legs, reported a difference in favour of closed-loop SCS in responder analysis and mean change in pain intensity. Although these trials demonstrate a significant reduction in pain intensity between baseline and follow-up across both arms, the blinding within them is to the intervention and not to the use of SCS; therefore, this does not add confidence regarding overall clinical effectiveness of SCS compared to standard (non-SCS) treatment.

DRGS stimulation is in scope of this PLR and was in scope for O'Connell (2021), although no studies of this stimulation type met their inclusion criteria. Therefore, the ACCURATE RCT (Deer 2017) is the best available evidence on these devices. The ACCURATE study demonstrated that DRGS may be more favourable than SCS for pain outcomes in patients with complex regional pain syndrome (CRPS).

Two large, appropriately adjusted, non-randomised studies were identified from sponsor and stakeholder submissions. Both were registry studies (Dhruva, 2023; Vu, 2022) that reported minimal differences in opioid consumption between large propensity matched cohorts (SCS compared to no SCS), none of which were considered clinically significant. Rates of implant removal or revision were 22.1% in Dhruva (2023). A major criticism of these studies is that patients in the SCS group are, by definition, further along in the treatment algorithm than the CMM patients, since they have failed CMM prior to qualifying for SCS.

For many clinical questions, propensity matched cohorts derived from large registry databases can provide powerful insights. However, the lengthy, multi-stepped nature of the clinical management pathway for chronic pain may not lend itself well to registry database analyses, which tend to lack granularity and specificity. However, if propensity matched cohorts are considered inadequate, then appropriate RCTs of high methodology quality will be even more vital to understanding the comparative effectiveness of SCS devices.

### **Clinical effectiveness – ischaemic pain**

The included Cochrane reviews (O’Connell 2021 and Traeger 2023) did not consider patients with ischaemic pain and no evidence for this indication was identified in the evidence scan or targeted consultation. Nevertheless, some descriptors for Medicare Benefits Schedule (MBS) items relating to SCS implantation services refer to ‘pain from refractory angina pectoris’ and therefore a NICE (2008) SR of SCS in people with ischaemic pain was included.

The review included eight RCTs (four for critical limb ischaemia [CLI] and four for angina). The findings were equivocal, and NICE did not recommend SCS for these indications.

### **Cost-effectiveness**

The available evidence on the comparative cost-effectiveness of SCS was provided by a SR by Niyomsri (2020), with only a single additional study identified in the peer-reviewed literature (Rojo 2021). Across these studies, the findings demonstrate that although initial costs of SCS devices are high, studies with longer time horizons tend to report that SCS is cost effective as the modelled improvement in health outcomes is extrapolated over this timeframe. The models were limited by a lack of long-term clinical data and missing follow-up costs.

An Australian cost-effectiveness study (commissioned by Neuromodulation Society of Australia and New Zealand [NSANZ]) was also identified (Deloitte 2019). A Markov model was used to compare treatments in FBSS and CRPS patients. The incremental cost-effectiveness ratio (ICER) was \$15,070 per QALY gained for patients with FBSS and \$2,321 per QALY gained for patients with CRPS.

The clinical evidence underpinning the Australian economic analysis is the PROCESS trial (Kumar 2007), which is an open-label RCT of SCS versus CMM in 100 patients with FBSS. The trial was included in both Cochrane reviews (O’Connell 2021; Traeger 2023). As these reviews noted, sham-controlled trials generally reported a smaller effect in favour of SCS than open-label trials. Furthermore, although the PROCESS study had follow-up to 2 years, extrapolation to 15 years introduces significant uncertainty with respect to both the durability of treatment effects and ongoing AE rates.

### **Patient selection and management**

No recent, high quality Australian clinical practice guidelines were identified in the search, although an Australian clinical algorithm was identified (Bates 2019). Most guidelines were consensus-based and the extent to which they would be applicable to Australian clinical practice is uncertain.

## **Considerations for MDHTAC**

Although triggered by AE reports (Jones et al. 2022), this PLR has focused on the comparative clinical effectiveness and cost-effectiveness of SCS with the understanding that the TGA is concurrently undertaking a post-market review and will consider safety.

The evidence base for the comparative clinical effectiveness of SCS compared to standard care is uncertain. Despite the large number of RCTs conducted of the devices, there remains doubt as to the magnitude of their clinical effect and the long-term risk of AEs. Given the clinical uncertainty, cost-effectiveness analysis to establish a suitable benefit for SCS devices is unlikely to be informative.

In light of the uncertainty in the evidence base for SCS, it is recommended that MDHTAC continue to list SCS devices on the PL, with no further increases in Benefit, whilst also undertaking further actions. The following actions are considered critical and are in line with the recommendations of the MBS Review Taskforce. To achieve these actions, MDHTAC may need to work with the TGA, MSAC, Australian Commission on Safety and Quality in Health Care (ACSQHC) and other stakeholders.

### 1. Development of high-quality clinical guidelines

The need for clinical guidelines for SCS devices was clearly articulated in the MBS Review Taskforce recommendations (2019) where it was noted that good outcomes were likely restricted to a very select patient population, and that patient selection and follow-up are critical but are difficult to include in an item descriptor. The development of clinical practice guidelines could bring together stakeholders, patients and clinical experts to fill a critical gap, bridging the uncertainty in the evidence with the need to make the best possible decisions in clinical practice. Furthermore, clinical practice guidelines can take a broader perspective on chronic pain treatment and management, with consideration of multidisciplinary approaches to patient care that address biological, psychological and social factors.

The development of any clinical guidelines needs to incorporate communication with MDHTAC and MSAC to ensure that listings are kept consistent with recommended clinical practice. For example, no evidence was found to support the use of SCS in refractory angina and this could be removed from MBS item descriptors if usage for this indication is not recommended in clinical guidelines.

### 2. Improved data monitoring and development of a national registry

The TGA clinical evidence guidelines on medical devices notes that device registries ‘play a unique and important role in medical device surveillance’<sup>1</sup>, noting the examples of the Australian Breast Device Registry (ABDR), the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) and the Victorian Cardiac Outcomes Registry (VCOR). Given the high cost, invasive nature and ongoing uncertainty regarding SCS, they are good candidates for inclusion within a registry.

Another option is to consider capturing SCS outcome data within the existing electronic Persistent Pain Outcomes Collaboration (ePPOC) initiative of the Faculty of Pain Medicine,<sup>2</sup> thereby allowing comparison of outcomes from SCS with non-surgical treatments.

In the absence of a national registry or extension to the ePPOC data collection, there is valuable information already available for monitoring the use of SCS devices and monitoring should be undertaken proactively. In particular, MBS data could be used to understand current patient profiles and links between insertions and removals (rates and timeframes). Consideration could be given to having a separate MBS item for implantable pulse generator (IPG) replacement due to battery end of life to differentiate this from removal due to lack of efficacy or other reasons. A similar MBS item exists for vagal nerve stimulation (item 40708) ‘surgical replacement of battery in electrical pulse generator’.

### 3. High-quality research

Conducting further trials of the same design will not resolve the outstanding uncertainty. Sponsors, researchers, and funders should all be encouraged to design studies that are methodologically rigorous, well conducted and reported, and answer priority questions. This may include the use of individual patient data or large registries, but it may also require a double blinded RCT of similar design to Hara (2022) using a different paraesthesia-free treatment arm.

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<sup>1</sup> Available at: <https://www.tga.gov.au/sites/default/files/clinical-evidence-guidelines-medical-devices.pdf>

<sup>2</sup> Available at: <https://www.uow.edu.au/ahsri/eppoc/>

There are a number of ongoing clinical trials of SCS and it is recommended that MDHTAC continue to monitor the outcomes of these.

These recommendations are supported by Pain Australia, the national peak body working to improve the quality of life of people living with pain, their families and carers. Pain Australia has recently undertaken a survey on consumer experiences of SCS that will be reported in late 2023 and should be considered by MDHTAC alongside the PLR.

Two PNS devices are currently listed on the PL in the same grouping as SCS. It is therefore recommended that MDHTAC:

- create a separate Group for PNS devices for chronic pain
- undertake focussed health technology assessment (HTA) of these devices to ensure they are appropriate for ongoing listing on the PL or refer them to MSAC for assessment
- consider the appropriateness of leads with dual approval for SCS and PNS indications.

## Considerations for MSAC

The MBS is legally enforceable and has greater scope than the PL for specifying conditions of use. The MBS Review Taskforce (2019) stated that:

“due to the evolving evidence regarding what population groups benefit from these procedures, these item numbers should be reviewed in 2 years to ensure ongoing evidence based applicability”

An MBS review is considered critical and is overdue. The review could consider the ongoing listing of SCS services on the MBS broadly and/or specific changes to the MBS items to improve monitoring and target appropriate claiming. Possible changes to MBS items are outlined below:

- The introduction of a separate MBS item for implantable pulse generator (IPG) replacement due to battery end of life (see recommendation 2).
- Clarification of the two MBS items for peripheral lead implantation
  - Surgical lead implantation has a higher benefit than percutaneous lead implantation. The item number for percutaneous lead implantation (39129) was introduced following the MBS Review Taskforce (2019), which identified no item for this purpose. However, utilisation is extremely low suggesting the surgical item continues to be claimed (see Figure 2). Sponsors have stated that surgical placement is not used for PNS.
- The introduction of, and mandated use of, item numbers for trial stimulation including the specification that trial leads be used.
- Removal of refractory angina as an indication for SCS, given the absence of evidence to support this indication. Alternately, creation of separate item numbers to monitor this indication.
- A restriction to once per lifetime for initial implantation of an SCS device.
- A requirement for a multidisciplinary team conference prior to initial implantation of an SCS device to discuss patient suitability for the intervention.

# 1 Background

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## 1.1 Context for the review

### 1.1.1 Prostheses List Post-Listing Review Framework

The Department of Health and Aged Care (DoHAC) has developed a working Post-Listing Review Framework<sup>3</sup> with the objective of addressing post-listing issues as required. This review is one of four trial reviews being conducted according to the framework with the outcomes to inform its further development.

## 1.2 About the spinal cord stimulators post-listing review

Spinal cord stimulators (SCS) are contained in Prescribed List (PL) Subcategory 04.05 Neurostimulation therapies for pain management. There have been no health technology assessments (HTA) conducted on SCS, with listing of Medicare Benefits Schedule (MBS) items relating to leads (insertion, repositioning, removal) and neurostimulators (placement and removal) occurring prior to the inception of Medical Services Advisory Committee (MSAC) (e.g., Item 39134 for neurostimulator placement was listed in 1993). These items, and the PL listings, cover both peripheral nerve stimulation (PNS) (via peripheral nerve lead placement, Items 39129 and 39138) and SCS (via epidural lead placement, Items 39139 and 39130).

### 1.2.1 Why review spinal cord stimulators?

A review based on analysis of Therapeutic Goods Association (TGA) adverse events (AEs) data raised concerns about long-term safety and effectiveness (Jones et al. 2022). Whilst expenditure on SCS pulse generators (04.05.01 Pulse Generators) has been relatively stable since 2016 (~\$30 million per year), they are a large expense in the Neurosurgical Category of the PL, with a total annual expenditure of ~\$55-60 million.

### 1.2.2 Undertaking the post-listing review

#### Analysis and evaluation of scientific literature, utilisation data, and additional relevant information

Health Research Consulting (hereco) was contracted by DoHAC to undertake the analysis and evaluation of the evidence. This review has been undertaken, in accordance with the 'PL Guide to Listing and Setting Benefits for Prostheses', to assess the comparative clinical effectiveness and cost-effectiveness of SCS, to review clinical practice guidelines for patient selection and management, and to advise the DoHAC on appropriate policy considerations for the continued investment of SCS listed on the PL.

The included services of this review can be found in Table 1.

**Table 1** Services to be provided in this PLR

Service	Description
1.	Determine which devices are in scope: <ul style="list-style-type: none"><li>Review the devices listed in the PL Subcategory - <i>04.05 Neurostimulation therapies for pain management</i> to identify those that are used or can be used for spinal cord stimulation and excluding peripheral, sacral and vagal nerve stimulators</li><li>Review the PLRT Utilisation Review of Spinal Cord Stimulators (incorporates Case Mix and MBS data) and accompanying agenda item provided to May 2022 PLAC and a copy of the PLAC advice</li></ul>

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<sup>3</sup> Available at: <https://www.health.gov.au/resources/publications/prostheses-list-post-listing-review-framework>

Service	Description
2.	<p>Assess the comparative clinical effectiveness of SCS compared to standard care, or alternative therapeutic approaches:</p> <ul style="list-style-type: none"> <li>Review the following key documents provided by DoHAC: <ul style="list-style-type: none"> <li>Information and submissions from sponsors</li> <li>Information and submissions from stakeholders (including relevant clinical guidelines)</li> <li>The TGA literature review that forms part of the TGA's post-market review of SCS (which incorporates key literature including the 2021 Cochrane review: Implanted spinal neuromodulation interventions for chronic pain in adults) and further TGA updates as available</li> <li>The 2022 Cochrane review: Spinal cord stimulation for low back pain if/when it becomes available</li> </ul> </li> <li>Undertake a search of key clinical trials registries (ANZCTR, Clinicaltrials.gov) for ongoing clinical trials which may provide relevant evidence in the short to medium term</li> <li>Undertake a search of HTA agencies for reviews of the comparative clinical effectiveness of SCS</li> <li>Undertake a highly targeted evidence scan for any pivotal clinical evidence not captured through the above sources</li> </ul>
3.	<p>Review the evidence base for the comparative cost-effectiveness of SCS:</p> <ul style="list-style-type: none"> <li>Review the following key documents provided by DoHAC: <ul style="list-style-type: none"> <li>Information and submissions from sponsors</li> <li>Information and submissions from stakeholders (including relevant clinical guidelines)</li> <li>The 2019 Deloitte report 'Cost effectiveness of pain devices' written for the 'Neuromodulation Society of Australia and New Zealand' and a complete budget impact model provided by Nevro Medical with consent to share</li> </ul> </li> <li>Conduct a targeted, systematic literature review of the evidence regarding cost-effectiveness of spinal cord stimulators</li> <li>Undertake a search of HTA agencies for reviews of the comparative clinical effectiveness of spinal cord stimulators</li> </ul>
4.	Review current CPGs for patient selection and management of SCS to treat chronic pain.
5.	<p>Summarise the knowledge/evidence base to address the following questions:</p> <ul style="list-style-type: none"> <li>What is the clinical effectiveness of SCS for the treatment of chronic pain compared to standard care or other therapeutic approaches?</li> <li>What evidence is available on the comparative cost-effectiveness of SCS for the treatment of chronic pain compared to standard care or other therapeutic approaches? Can any conclusions be drawn from the evidence base?</li> <li>What evidence-based CPGs are available for patient selection and management of SCS? If key guidelines are identified, what recommendations do they make?</li> </ul>
6.	Guided by the PL Post-Listing Review Framework, present the information and evidence from services 1 to 5 in a report to support the Department to assess what actions or policy initiatives should be considered with regards to devices used for SCS for chronic pain.

Abbreviations: ANZCTR, Australian New Zealand Clinical Trials Registry; CPGs, clinical practice guidelines; DoHAC, Department of Health and Aged Care; HTA, health technology assessment, PL, Prostheses List; PLAC, Prostheses List Advisory Committee; PLR, post-listing review; PLRT, Prostheses List Reform Taskforce; SCS, spinal cord stimulation; TGA, Therapeutic Goods Administration

## Targeted consultation

Sponsors and stakeholders were invited to submit information for the post-listing review (PLR) on the following questions:

- The PLR is considering SCS, which treat chronic pain by delivering electrical impulses via leads placed in the epidural space. The following devices are outside scope of this review: PNS, sacral nerve stimulators (SNS) and vagal nerve stimulators (VNS). Do you have any comments on the scope of the review? If you are a sponsor, which of your devices are within scope for the review?
- The PLR will consider the evidence from the 2021 Cochrane Review (O'Connell et al.). Is there additional evidence on the comparative clinical effectiveness of SCS compared to standard care, or alternative therapeutic approaches? Studies must be comparative (randomised or appropriately

adjusted) include patient-relevant outcomes and have at least medium (4-8 months) and preferably, long-term ( $\geq 12$  months) follow-up.

3. Is there evidence for the comparative cost-effectiveness of SCS?
4. Are there any ongoing trials which may impact the findings of the PLR?
5. What guidelines are available to guide patient selection and the management of SCS to treat chronic pain?

In addition to these questions, the review scope was also circulated to sponsors and stakeholders on 16<sup>th</sup> December 2022, with submission due on 15<sup>th</sup> February 2023.

## 1.3 Spinal cord stimulators for chronic pain

### 1.3.1 Description of the condition

Chronic pain is classified as pain that persists for more than three months or extends beyond the period of disease or the expected recovery time (Deloitte 2019; NICE 2008). The 2008 NICE guideline (TA159) states that “chronic pain is accompanied by physiological and psychological changes such as sleep disturbances, irritability, medication dependence and frequent absence from work”. Chronic pain affects 3.24 million Australians<sup>4</sup> and was estimated to cost \$73.2 billion in 2018, including health system costs and productivity losses (Deloitte 2019). Additionally, Australians living with chronic pain experience a substantial reduction in quality of life, with adverse effects on their physical and mental wellbeing (O’Connell et al. 2021).

The development of chronic pain is heterogenous, with a variety of causes including clearly identifiable nociceptive pain conditions, such as rheumatoid arthritis, and neuropathic pain as a result of nerve trauma. In other cases, such as chronic low back pain and fibromyalgia, the causes behind chronic pain remain unclear and could be attributed to a variety of pathological mechanisms (O’Connell et al. 2021). The latest revision of the World Health Organisation’s (WHO) International Classification of Diseases (ICD), the ICD-11 (2022), has recognised chronic pain as a standalone health condition that is characterised by disability and distress, in addition to classification as a secondary symptom to other underlying health conditions<sup>5</sup> (O’Connell et al. 2021).

### 1.3.2 Description of the intervention

#### Neurostimulation therapies

Neurostimulation therapies are used to alleviate a number of health conditions and symptoms, including seizures, movement disorders and chronic pain, by targeting the signals sent to the brain or nervous system. These devices work by delivering electrical stimulation to various neural targets and are often a last line treatment after other therapies have failed due to their invasive nature. Neurostimulation therapies currently available in Australia include deep brain stimulation (DBS), SCS, SNS and VNS.

All neuromodulation therapy devices comprise of three main components – a pulse generator, a patient programmer, and leads with integrated electrodes.

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<sup>4</sup> Data from 2018 (Deloitte 2019)

<sup>5</sup> See <https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1581976053>

## Spinal cord stimulators

### Pulse generators

There are currently 18 pulse generators listed on the PL (November 2022) (Table 2) in Group 04.05.01 Pulse Generators under the 'Neurostimulation Therapies for Pain' Subcategory. The Group includes a heterogeneous list of devices that are not restricted to SCS. These devices, however, are all broadly used for the treatment of chronic pain although there are differences in both their mode of action and the specific types of chronic pain they are used to treat.

**Table 2 Pulse generators listed in Group 04.05.01 of the Neurosurgical Category in the PL (November 2022)**

Type	Device	Sponsor	ARTG Number	GMDN Code	Billing Code	Benefit
SCS	Precision Novi IPG	Boston Scientific	283692	36007 Stimulator, electrical, analgesic, spinal cord	BS322	\$21,660
SCS	WaveWriter Alpha	Boston Scientific	362970; 362971	36007 Stimulator, electrical, analgesic, spinal cord	BS383	\$21,660
SCS	Proclaim IPG	Abbott Medical	279015; 279016	36007 Stimulator, electrical, analgesic, spinal cord	SJ379	\$21,660
SCS	Proclaim XR IPG	Abbott Medical	351631; 351632	36007 Stimulator, electrical, analgesic, spinal cord	SJ432	\$21,660
SCS	PrimeAdvanced Surescan MRI Neurostimulator	Medtronic	215751	36007 Stimulator, electrical, analgesic, spinal cord	MI135	\$17,283
SCS	Intellis AdaptiveStim Neurostimulator	Medtronic	298746	36007 Stimulator, electrical, analgesic, spinal cord	MI274	\$23,465
SCS	Evoke Closed Loop Stimulator (CLS)	Saluda Medical	336330	64970 Analgesic spinal cord electrical stimulation system pulse generator implantable	UY003	\$23,465
SCS	Precision Spectra IPG	Boston Scientific	205793	36007 Stimulator, electrical, analgesic, spinal cord	BS254	\$23,465
SCS	Precision Spectra WaveWriter IPG	Boston Scientific	318260	36007 Stimulator, electrical, analgesic, spinal cord	BS362	\$23,465
SCS	WaveWriter Alpha	Boston Scientific	362972; 362973	36007 Stimulator, electrical, analgesic, spinal cord	BS389	\$23,465
SCS	Precision Montage MRI IPG	Boston Scientific	286709	36007 Stimulator, electrical, analgesic, spinal cord	BS330	\$23,465
SCS	Prodigy IPG	Abbott Medical	230721; 279911	36007 Stimulator, electrical, analgesic, spinal cord	SJ374	\$23,465
SCS	Senza II IPG Kit	Emergo Asia	186043	36007 Stimulator, electrical, analgesic, spinal cord	ER496	\$23,465
SCS	Senza Omnia IPG Kit	Emergo Asia	330704	36008 Stimulator, electrical, analgesic, spinal cord	ER535	\$23,465
SCS	Vanta™ Recharge-Free Neurostimulator	Medtronic	386887	64970 Analgesic spinal cord electrical stimulation system pulse generator implantable	MI495	\$19,088
DRGS	Proclaim DRG	Abbott Medical	289235; 333461	36007 Stimulator, electrical, analgesic, spinal cord	SJ389	\$21,660
MBNS	Reactiv8 Implantable Pulse Generator	Mainstay Medical	327089	62422 Implantable lumbar neuromuscular electrical stimulation system pulse generator	PQ004	\$17,283
PNS	StimRouter Neuromodulation System Kit	Algotim Research and Development	313344	38474 Stimulator, electrical, analgesic, peripheral nerve, implantable	FP001	\$18,032



Abbreviations: ARTG, Australian Registry of Therapeutic Goods; DRGS, dorsal root ganglion stimulation; GMDN, Global Medical Device Nomenclature; MBNS, medial branch nerve stimulation; PL, Prostheses List; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation. Note: ARTG numbers are current according to Public Summary Documents (TGA)

Fifteen of the 18 pulse generators are true SCS that target the nerves in the epidural spaces along the spinal column. The targets for SCS vary along the spinal column and are dependent on the source of the pain. For example, in order to alleviate pain caused by failed back surgery syndrome (FBSS), the target for electrical stimulation would generally be the lower thoracic spine (Moore et al. 2016).

One of the other three pulse generators on the PL is the Proclaim DRG (Abbott Medical), which is a dorsal root ganglion stimulator (DRGS). This device stimulates the dorsal root ganglion structures that are located under the vertebral pedicle at the thoracic and lumbar levels (Ahimsadasan et al. 2022). The dorsal root ganglion is an accessible bundle of sensory nerves in the epidural space where each nerve transmits sensory messages from a defined target in the body, such as the hand, foot, knee, or chest. Due to its easy accessibility and ability to target a specific part of the body, DRGS systems are often used in areas that are hard to treat using SCS systems (Deer et al. 2019).

Another of the listed devices is a medial branch nerve stimulator (MBNS) by Mainstay Medical called Reactiv8. Reactiv8 targets the peripheral nerves in the multifidus muscle for the treatment of axial chronic low back pain. In order to alleviate pain, Reactiv8 uses implanted leads and an IPG to deliver electrical stimulation to the dorsal ramus nerve to induce contraction of the multifidus muscle (Mainstay Medical 2022)<sup>6</sup>.

The remaining device is the StimRouter Neuromodulation System (Algostim), which stimulates peripheral nerves in multiple locations around the body. Unlike the other devices in this Subcategory, the StimRouter Neuromodulation System has an external pulse transmitter (EPT) which sits outside the body (not implanted) and is synonymous with the IPG from the other neurostimulation systems.

#### Leads, external components and accessories

The remaining components of these systems are listed in separate Groups in the PL, except for Algostim's Stimrouter Neuromodulation System which is listed as a kit. The list of components can be found in Appendix A, Table App 1. There are 45 leads and lead extensions listed in Groups 04.05.03 (Leads) and 04.05.04 (Lead Extension). Amongst these, there are three leads pertaining to Abbott's DRG system; however, two are attributed to the de-listed Axium Neurostimulator. There is also one lead for the Reactiv8 MBNS system.

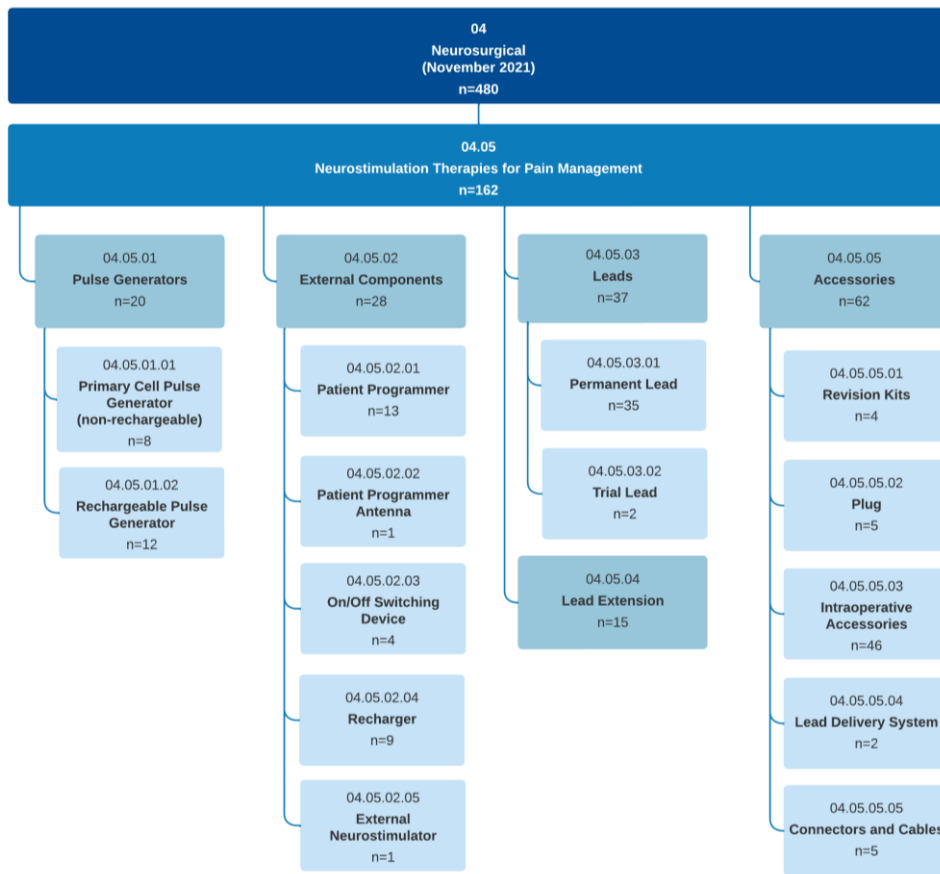
Eleven external component devices, including the patient programmer and rechargers, are listed in Group 04.05.02 (External Components). Two of these devices pertain to the Reactiv8 MBNS system, and one is for the delisted DRGS Axium Neurostimulator. The patient programmer for Abbott's Prodigy DRG is the same as for the SCS systems. Lastly, there are 71 devices listed in Group 04.05.05 (Accessories); these are additional components to the SCS, DRGS, PNS, and MBNS systems, including revision kits and intraoperative accessories.

Figure 1 shows the organisation of neuromodulation systems on the November 2021 PL.

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<sup>6</sup> <https://mainstaymedical.com/physicians/>

**Figure 1 PL organisation of SCS, DRGS, MBNS, and PNS systems (November 2021)**



### Devices for review

Given the heterogeneity of the devices in the Groups within the Neurostimulation Therapies for Pain Management Subcategory, the devices to be formally included in this PLR are identified and discussed in Section 2. The decisions regarding device inclusion are based on stakeholder feedback and consideration of existing documentation.

## 2 Devices within scope

The research question to focus the review is:

*Review the devices listed in the PL Subcategory - 04.05 Neurostimulation therapies for pain management - to identify those that are used or can be used for spinal cord stimulation, and excluding peripheral, sacral and vagal nerve stimulators.*

The approach taken to identify the devices in scope for this PLR involved a review of the literature provided by DoHAC, consideration of sponsor and stakeholder feedback, while ensuring consistency with TGA activities and Prostheses List Advisory Committee (PLAC) advice.

### 2.1 Stakeholder and sponsor feedback

#### 2.1.1 Sponsors

All devices listed in Group '04.05.01 Pulse Generators' (November 2022) under the Subcategory 'Neurostimulation Therapies for Pain' are listed in Table 3. Sponsors were requested to confirm which of their devices they considered to be within scope of this review. The responses are tabulated below and devices that are green are true SCS devices and clearly in scope for the review.

Three devices (all described in Section 1.3.2) required further consideration: a DRGS (shown in yellow) and two PNS devices (orange). Sponsors for the two PNS devices consider their devices out of scope.

**Table 3 Pulse generators listed in Group 04.05.01 of the Neurosurgical Category in the PL (November 2022)**

Type	Device	Sponsor	Billing Code	Sponsor confirmed device as 'in scope'?
SCS	Precision Novi IPG	Boston Scientific	BS322	NR
SCS	WaveWriter Alpha	Boston Scientific	BS383	NR
SCS	Proclaim IPG	Abbott Medical	SJ379	NR
SCS	Proclaim XR IPG	Abbott Medical	SJ432	NR
SCS	PrimeAdvanced Surescan MRI Neurostimulator	Medtronic	MI135	✓
SCS	Intellis AdaptiveStim Neurostimulator	Medtronic	MI274	✓
SCS	Evoke Closed Loop Stimulator (CLS)	Saluda Medical	UY003	✓
SCS	Precision Spectra IPG	Boston Scientific	BS254	NR
SCS	Precision Spectra WaveWriter IPG	Boston Scientific	BS362	NR
SCS	WaveWriter Alpha	Boston Scientific	BS389	NR
SCS	Precision Montage MRI IPG	Boston Scientific	BS330	NR
SCS	Prodigy IPG	Abbott Medical	SJ374	NR
SCS	Senza II IPG Kit	Emergo Asia	ER496	NR
SCS	Senza Omnia IPG Kit	Emergo Asia	ER535	NR
SCS	Vanta™ Recharge-Free Neurostimulator	Medtronic	MI495	✓
DRGS	Proclaim DRG	Abbott Medical	SJ389	NR
MBNS	Reactiv8 Implantable Pulse Generator	Mainstay Medical	PQ004	✗
PNS	StimRouter Neuromodulation System Kit	Algostim Research and Development	FP001	✗

Abbreviations: ARTG, Australian Registry of Therapeutic Goods; DRGS, dorsal root ganglion stimulation; MBNS, medial branch nerve stimulation; NR, not responded; PL, Prostheses List; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.

## 2.1.2 Stakeholders

Stakeholders provided limited feedback on the devices they considered in scope. One stakeholder considered all implanted neuromodulation devices for pain to be in scope, regardless of whether they stimulate the spinal cord or peripheral nerves.

## 2.2 Other considerations

### 2.2.1 TGA review

The TGA is undertaking a post-market review of SCS devices<sup>7</sup> and states that the review includes:

- spinal cord implantable stimulation leads;
- spinal cord implantable impulse generators;
- peripheral spinal nerve implantable stimulation leads; and
- peripheral spinal nerve implantable impulse generators.

This wording would include SCS, DRGS and MBNS devices but exclude StimRouter, which is implanted in a wide variety of peripheral locations.

### 2.2.2 MBS items and utilisation of spinal cord stimulators

The MBS items applicable to SCS and PNS are listed in Appendix B, Table App 2. The key MBS item for IPG implantation is 39134, which is for connection to 'epidural or peripheral nerve electrodes for the management of chronic neuropathic pain or pain from refractory angina pectoris.' Based on utilisation data for MBS item 39134, IPG insertions are estimated to be around 1,300 to 1,500 per year and removals, based on MBS item 39135, around 400 to 500 per year.

There are different MBS items for PNS peripheral nerve lead placement (items 39129 [percutaneous placement] and 39138 [surgical placement]) and SCS epidural lead placement (items 39130 [percutaneous placement] and 39139 [surgical placement]), both for the management of chronic neuropathic pain. These items underwent changes in March 2022<sup>8</sup> to clarify that the use of Percutaneous Electrical Nerve Stimulation (PENS) procedures for chronic pain cannot be billed under the MBS and the item 39129 for percutaneous peripheral lead placement was introduced.

MBS utilisation data shows a similar pattern of claims for both percutaneous epidural placement (SCS) and surgical peripheral placement (PNS) (Figure 2, noting there was no item for percutaneous peripheral placement until March 2022). The data show utilisation of peripheral lead placement to be around 500 to 1,000 claims lower than epidural placement per financial year from 2014-15. The MBS items distinguish between PNS and SCS procedures for chronic pain but do not distinguish between on-label and off-label use of the leads for these procedures.

The claims against MBS item 39138 up until mid-2019 do not reflect utilisation of the PNS devices listed on the PL as these devices were only listed from July 2019 (StimRouter) and from July 2020 (Reactiv8). Rather they may reflect both use for PENS procedures (up until 2022), use of percutaneous leads with approval for both PNS and SNS (see Appendix B), and off-label peripheral use with percutaneous SCS leads which was raised in stakeholder feedback.

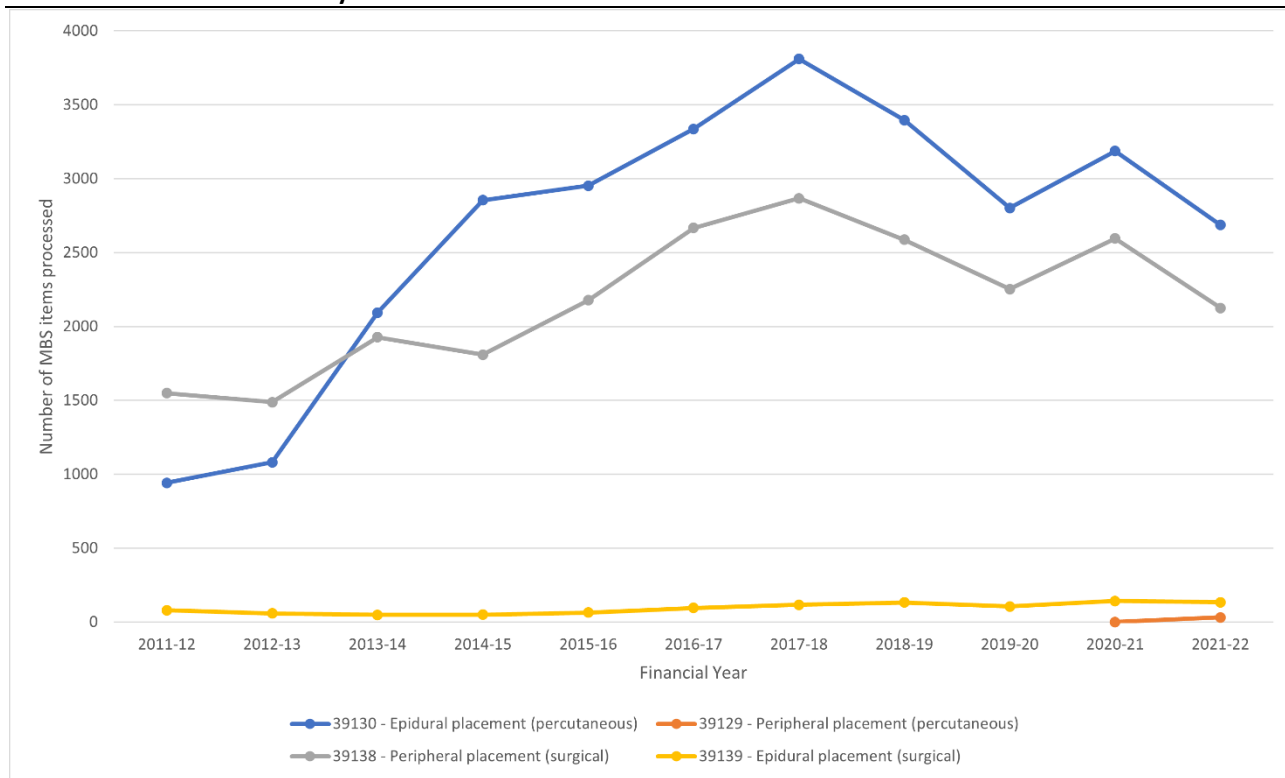
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<sup>7</sup> See <https://www.tga.gov.au/post-market-reviews/post-market-review-spinal-cord-stimulation-scs-devices>

<sup>8</sup> See [http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/77B4A4137E501F71CA2587B1007CAC2F/\\$File/Factsheet-Implanted-Device-Procedure-MBS-changes.12.04.22.pdf](http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/77B4A4137E501F71CA2587B1007CAC2F/$File/Factsheet-Implanted-Device-Procedure-MBS-changes.12.04.22.pdf)

An application for listing of PENS on the MBS, by modifying the restriction on items 39129 and 39128, has been received by MSAC<sup>9</sup>.

**Figure 2** Number of MBS items processed for epidural and peripheral placement of neurostimulator leads for financial years 2011-12 to 2021-22



Source: Data from Medicare item reports available at: [http://medicarestatistics.humanservices.gov.au/statistics/mbs\\_item.jsp](http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp)

In addition to the introduction of item 39138, Explanatory Note TN 8.2.44 (Appendix B) was also added to MBS items for SCS to inform “best practice and effective use of the health system”. The MBS Review Taskforce (2019) recommended the addition of TN 8.2.44 based on the following assessment:

- *Implantable devices may be an effective and cost effective pain management intervention in a very select patient population. There is a high risk of poor outcomes and lack of cost effectiveness with inadequate patient selection and follow up (International Neuromodulation Society 2017). It is difficult to modify the descriptors to contain all the criteria needed for a good patient outcome and this is not generally included in a descriptor. In addition, evidence continues to evolve regarding patients who may benefit from these procedures.*
- *Clinical guidelines for implantable devices for pain management are currently under development by the Faculty of Pain Medicine and should be incorporated in the notes when available.*
- *It was considered that outlining high level best clinical practice in the explanatory notes would be helpful in guiding clinical practice and patient selection.*
- *Due to evolving evidence, it is recommended that these item numbers be reviewed in 2 years to ensure ongoing evidence-based applicability.*

<sup>9</sup> Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1739-public>

## 2.3 Analysis

The three devices for further consideration are compared to a representative SCS device (Proclaim IPG) in Table 4. All are pulse generators for the treatment of chronic pain. Unlike the other devices, the StimRouter pulse generator is not implantable and therefore the TGA risk class for this device is lower.

**Table 4 Comparison of a representative SCS device with the listed DRGS, MBNS and PNS devices**

Type	Device (Sponsor)	Intended Purpose	Within TGA review scope	GMDN Code	Risk Class
SCS	Proclaim IPG (Abbott Medical)	Spinal cord stimulation (SCS) systems are indicated as an aid in the management of chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back and leg pain.	✓	36007 Stimulator, electrical, analgesic, spinal cord	AIMD
DRGS	Proclaim DRG (Abbott Medical)	Indicated for spinal column stimulation via epidural and intraspinal lead access to the dorsal root ganglion as an aid in the management of moderate to severe chronic intractable pain of the lower limbs in adult patients with complex regional pain syndrome (CRPS) types I and II.	✓	36007 Stimulator, electrical, analgesic, spinal cord	AIMD
MBNS	Reactiv8 Implantable Pulse Generator (Mainstay Medical)	The ReActiv8 System is indicated for bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the transverse process at L3 as an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction, as evidenced by imaging or physiological testing in adults who have failed therapy including pain medications and physical therapy and are not candidates for spine surgery.	✓	62422 Implantable lumbar neuromuscular electrical stimulation system pulse generator	AIMD
PNS	StimRouter Neuromodulation System Kit (Algotim Research and Development)	The StimRouter Neuromodulation System is indicated for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as an adjunct to other modes of therapy (e.g., medications). The StimRouter is not intended to treat pain in the craniofacial region.	✗	38474 Stimulator, electrical, analgesic, peripheral nerve, implantable	IIB

Sources: Product IFUs, TGA entries, PL entries

Abbreviations: AIMD, active implantable medical device; DRGS, dorsal root ganglion stimulator; GMDN, Global Medical Device Nomenclature; IPG, implantable pulse generator; MBS, Medicare Benefits Schedule; MBNS, medial branch nerve stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation; TGA, Therapeutic Goods Administration

### Dorsal root ganglion stimulation (Proclaim DRG)

DRGS devices are considered within scope for this review. Their target location is similar to that of SCS devices; both target the epidural space of the spinal column, however DRGS leads are limited to the space under the vertebral pedicle at the thoracic and lumbar levels. While this allows for a more targeted neural focus, particularly in patients with refractory chronic neuropathic pain and focal pain (Rigoard et al. 2022), the target for stimulation remains in the spinal column and is therefore appropriate for inclusion when reviewing SCS. DRGS and SCS systems will be referred to as 'SCS' for the remainder of this review.

### Medical branch nerve stimulation (Reactiv8 Implantable Pulse Generator)

The MBNS device is specifically indicated for chronic low back pain associated with multifidus muscle dysfunction. It targets the medial branch of the dorsal ramus and would likely be included in the TGA review on the basis of this being a peripheral spinal nerve. However, the sponsor considers the device out

of scope for the review and unlike SCS and DRGS devices, it is not implanted into the epidural space of the spinal cord. The device is considered out of scope for the review, given it is not targeting the spinal cord.

MBNS devices may be expected to have different clinical effectiveness and safety outcomes compared to SCS devices and would need to be evaluated separately. NICE evaluated these devices in 2022 (NICE 2022) and concluded that:

*‘Evidence on the efficacy and safety of neurostimulation of lumbar muscles for refractory non-specific chronic low back pain is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.’*

## Peripheral nerve stimulation (StimRouter Neuromodulation System Kit)

The PNS device, StimRouter, can be used to target different peripheral nerves around the body depending on the site of the pain. It differs significantly from the other devices and is out of scope for the review. It would also be out of scope for the TGA review. Two systematic reviews (SRs) of PNS were identified in the evidence scan (Wong et al. 2022; Helm et al. 2021).

## 2.4 Conclusions/Summary

The devices in scope for the review are SCS and DRGS devices. These devices are shaded in green and yellow in Table 3. The MBNS and PNS devices shaded orange are out of scope and are not considered in the comparative clinical effectiveness or cost-effectiveness analysis. Therefore, the PL Group ‘04.05.01 Pulse Generators’ will not have been reviewed in its entirety. The two out of scope devices have not been subject to HTA in Australia through either the MSAC or PLAC/MDHTAC processes and consideration should be given both to whether they should undergo assessment and whether they should remain in the same Group as SCS devices.

## 3 Comparative clinical effectiveness

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### 3.1 Methodology

The research question to focus the review is:

*What is the clinical effectiveness of SCS for the treatment of chronic pain compared to standard care or other therapeutic approaches?*

This was assessed using a rapid review methodology. The review utilises existing SRs and includes primary studies only where gaps in the evidence base are apparent. The approach to evidence identification is multipronged consisting of:

- targeted evidence scan;
- key documents supplied by DoHAC (see Table 1), sponsors and stakeholders.

Details of the methodology are provided in Appendix C.

#### 3.1.1 Targeted evidence scan

A rapid search of the peer-reviewed scientific literature and the grey literature was conducted (Appendix C, Section C.1.1). A pragmatic approach was taken with a focus on identifying the most comprehensive, high quality, and recent SRs that addressed the study question, and supplementing this with additional studies if necessary. Following this evidence scan, O'Connell (2021) published by the Cochrane Collaboration was identified as the most recent, applicable, and comprehensive evidence source. As a Cochrane review, it is subject to high editorial standards and is considered at low risk of bias.

During preparation of this review, a second study published by the Cochrane Collaboration (Traeger 2023) was published. These two SRs were selected as key studies. O'Connell (2021) considered SCS for chronic neuropathic pain whilst Traeger (2023) was restricted to studies in patients with low back pain. A third SR (NICE 2008) has been included to consider SCS in ischaemic conditions.

#### 3.1.2 Studies from stakeholder submissions

Stakeholders were invited to submit evidence that addressed the research questions of the review, and this evidence was collated (Appendix C, Section C.1.2) and reviewed for inclusion alongside the key studies identified in the targeted evidence scan. Comparative studies with medium to long-term follow-up, reporting on outcome consistent with the key studies were identified for inclusion.

#### 3.1.3 Methodological considerations for undertaking research in SCS

The gold standard for the assessment of any medical treatment is a double-blind randomised controlled trial (RCT) and this is the preferred study design for HTA assessment (MSAC Guidelines<sup>10</sup>) and the Cochrane Collaboration<sup>11</sup>. However, there are known challenges<sup>11</sup> in the design and conduct of such trials in medical devices (Haute Autorité De Santé 2021<sup>12</sup>) and identifying the most robust evidence can be complex.

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<sup>10</sup> [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/E0D4E4EDDE91EAC8CA2586E0007AFC75/\\$File/MSAC%20Guidelines-complete-16-FINAL\(18May21\).pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/E0D4E4EDDE91EAC8CA2586E0007AFC75/$File/MSAC%20Guidelines-complete-16-FINAL(18May21).pdf)

<sup>11</sup> <https://training.cochrane.org/handbook/current/chapter-03#a-33-determining-which-study-designs-to-include>

<sup>12</sup> [https://www.has-sante.fr/upload/docs/application/pdf/2021-09/guide\\_methodology\\_for\\_the\\_clinical\\_development\\_of\\_md.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2021-09/guide_methodology_for_the_clinical_development_of_md.pdf)



The clinical effectiveness of SCS has been studied over a long period and there are many published RCTs, yet interpretation of their findings is challenging and there are methodological considerations that should be noted.

Medical devices are known to undergo continuous incremental change, and this is evident in the design of SCS devices, which now have a broad range of settings, stimulation parameters, features and programming algorithms. This review considers SCS devices compared to ‘standard care or other therapeutic approaches’, which aligns with the PICOs considered by the Cochrane reviews (O’Connell 2021; Traeger 2023) but may not reflect the trial designs requested for regulatory approval, thereby omitting more recent evidence. Furthermore, due to the difficulty of blinding participants and treating clinicians, RCTs that compare two types of SCS could be of a higher methodological quality than unblinded or open-label studies, which can have biases in patient selection, follow-up, attrition, and measurement. In the absence of appropriate blinding, an objective outcome measure is preferred; however, SCS devices are designed to treat chronic pain, which is subjective and is the primary outcome in the majority of studies. Finally, SCS devices are designed to be implanted long term and therefore the durability of their effect, and the rate and risk of long-term complications, are critical considerations in assessing their comparative clinical effectiveness; however, many RCTs were of short duration.

The evidence scan identified studies that reported on methodological considerations in the SCS trials (Katz 2021; McNicol 2021; Duarte 2020). McNicol (2021) highlights the concerns raised above, noting that of 46 studies included in their review of RCTs for SCS, 11 blinded the participants, of which only five were assessed as adequately blinded. The median study duration was 12 weeks and 87% had a pain-related primary outcome. Both Katz (2021) and Duarte (2020) provide recommendations for undertaking RCTs of SCS, with Katz providing recommendations for outcome measures and reporting, and Duarte providing a checklist for reporting on a placebo arm.

In light of these methodological considerations, this review reports on the Cochrane SRs and then incorporates additional evidence identified by sponsors and stakeholders in an effort to present a considered overview of the best available evidence.

## 3.2 Summary of the evidence

### 3.2.1 Included Cochrane review (Traeger 2023)

Traeger (2023) evaluated the effects, including the benefits and harms, of SCS for people with low back pain, with or without leg pain. Patients who had chronic low back pain as a result of serious spinal pathology were excluded. The SR assessed SCS by evaluating RCTs that compared:

- SCS versus placebo;
- SCS plus medical management versus medical management alone.

To facilitate analysis, the SR categorised tonic stimulation below 1 kHz as ‘conventional SCS’, tonic stimulation between 1 kHz and 10 kHz as ‘high frequency’, and intermittent bursts of stimulation as ‘burst’. The data were reported on across four different time points – immediate term (< 1 month), short term (≥ 1 month to < 3 months), medium term (≥ 3 months to <12 months), and long term (≥ 12 months). The major outcomes assessing benefits were pain intensity, function, health-related quality of life (HRQoL), and global assessment of efficacy. The major outcomes assessing harms were proportion of withdrawals due to AEs, proportion of participants with AEs, and proportion of participants with serious adverse events (SAEs). The minor outcomes were medication use, health care use, and work status. The study characteristics are summarised in Table 5.

**Table 5 Study characteristics of Traeger (2023)**

Study ID	Search dates	Patient population	Interventions	Comparator	Outcomes	Time points
Traeger 2023 Cochrane Review	Inception to 10 June 2022	Participants ≥ 18 yrs old with chronic low back pain (> 12 wks pain duration), with or without leg pain, including patients with FBSS	1. SCS 2. SCS + medical management	1. Placebo 2. Medical management	<u>Major Harms:</u> withdrawals due to AEs; AEs; SAEs <u>Benefits:</u> Pain intensity; function; HRQoL; global assessment of efficacy <u>Minor Medication use;</u> health care use; work status	Immediate term: < 1 month Short term: ≥ 1 month to < 3 months Medium term: ≥ 3 months to <12 months Long term: ≥ 12 months

Abbreviations: AE, adverse event; FBSS, failed back surgery syndrome; HRQoL, health-related quality of life; SAEs, severe adverse events; SCS, spinal cord stimulation.

## Included studies

Thirteen published RCTs with 699 participants met the inclusion criteria (Table 6). The trials included patient populations with a range of low back pain indications including FBSS, (complex regional pain syndrome) CRPS, radicular leg pain, and chronic low back pain. Ten of the thirteen RCTs were cross-over studies ranging from 4 to 50 participants, and the remaining three RCTs were parallel studies ranging from 100 to 218 participants. Six of the RCTs declared industry funding. One study, PROCESS, included Australian sites.

**Table 6 Characteristics of studies included in Traeger (2023)**

Study ID	Design	Participants N	Intervention Comparator	Outcomes	Funding COI	Treatment duration
Rigoard 2019 (PROMISE)	Parallel RCT	FBSS 218	SCS (conventional) OMM	Pain intensity; function; HRQoL	Medtronic NR	24 mo
Kumar 2007 (PROCESS)	Parallel RCT	FBSS 100	SCS (conventional) +CMM CMM	Pain intensity; HRQoL; function; medication use; AEs	Medtronic NR	12 mo
Kapurall 2022	Parallel RCT	Chronic, refractory axial low back pain 159	SCS (HF) CMM	Pain intensity; daily dose opioids; opioid usage; AEs; HRQoL; work status; healthcare use	Nevro Corp Yes	6 mo
Hara 2022	Cross-over RCT	Chronic radicular pain 50	SCS (burst) Sham	Pain intensity; physical function; QoL; surgical revisions and AEs	Liaison Committee for Education, Research and Innovation NR	3 mo per treatment
Al-Kaisy 2018	Cross-over RCT	FBSS 30	SCS (HF) Sham	Pain intensity, AEs	Medtronic NR	3 wks per treatment
Eldabe 2020	Cross-over RCT	FBSS 19	SCS (burst, conventional) Sham	Pain intensity; HRQoL; safety	Medtronic NR	2 wks per treatment

Study ID	Design	Participants N	Intervention Comparator	Outcomes	Funding COI	Treatment duration
Perruchoud 2013	Cross-over RCT	Chronic low back pain 38	SCS (HF) Sham	Pain intensity, HRQoL; AEs; medication use	Medtronic Medtronic	2 wks per treatment
Sokal 2020	Cross-over RCT	FBSS; CRPS 18	SCS (conventional, burst, HF) Sham	Pain intensity; function; medication use; complications	No Yes	2 wks per treatment
Sweet 2016	Cross-over RCT	Post-laminectomy syndrome with low back pain 4	SCS (conventional) Sham	Pain intensity	No Yes	2 wks per treatment
Schu 2014	Cross-over RCT	FBSS 20	SCS (conventional, burst) Sham	Pain; function; safety (AEs)	No Yes	1 wk per treatment
De Ridder 2013	Cross-over RCT	FBSS 15	SCS (burst, conventional) Sham	Pain intensity	NR Yes	1 wk per treatment
Wolter 2012	Cross-over RCT	Neuropathic pain 10	SCS (conventional) Sham	Pain intensity	No No	1 wk per treatment
Eisenberg 2015	Cross-over RCT	Radicular leg pain 18	SCS (conventional) Sham	Clinical (radicular) pain	NR No	2 hrs per treatment

Abbreviations: AE, adverse event; CMM, conventional medical management; COI, conflicts of interest; CRPS, complex regional pain syndrome; EQ-5D, EuroQOL 5-dimension questionnaire; FBSS, failed back surgery syndrome; HF, high-frequency; hrs, hours; HRQoL, health-related quality of life; mo, months; NR, not reported; OMM, optimal medical management; QoL, quality of life; RCT, randomised controlled trial; SCS, spinal cord stimulation; wk(s), weeks.

The authors considered that all three parallel-group RCTs were at high risk of performance and detection bias due to lack of blinding, three of the cross-over RCTs were considered adequately blinded whereas the remaining seven were at either unclear or high risk. Eleven of the 13 trials (84%) were judged to be at unclear or high risk of selective reporting bias, and twelve (92%) were at risk of other potential bias predominately due to failure to describe methods used to account for carryover and period effects in cross-over studies.

The ten cross-over RCTs compared SCS with sham treatment (e.g. device is switched off, switched to low amplitude, discharging without transmitting to the lead etc.). The three parallel trials evaluated the addition of SCS to conventional medical management (CMM). The parallel trials were not initially eligible for inclusion based on the pre-specified criteria of 'no intervention' as a comparator; however, the authors have ultimately included these studies.

The SR characterised the type of frequency stimulation for the included RCTs; nine studies delivered conventional frequency stimulation, five studies delivered high-frequency stimulation, and five studies delivered burst stimulation. Four studies included SCS systems that delivered more than one type of frequency stimulation. Seven studies required participants to already be implanted with an SCS and have achieved stable pain control.

Thirteen ongoing studies evaluating SCS were identified in the SR and are listed in Table App 5 and Table App 6.

## Findings

### Spinal cord stimulation versus placebo (sham stimulation)

Nine of the ten cross-over RCTs that compared SCS with sham stimulation reported immediate term outcomes (at less than one month). Eight were eligible for pooling in a meta-analysis; Eisenberg (2015) measured outcomes on the same day and was excluded.

One sham-controlled study reported a treatment period of three months (Hara 2022); therefore the outcomes are classified by the review as medium term.

AEs were poorly reported in the sham trials and given all participants were implanted with an SCS device, they do not provide comparative data on AEs.

#### Pain intensity

There was evidence in favour of SCS compared to sham at less than one month follow-up in reducing pain intensity (mean difference (MD) -13.8, 95% confidence interval (CI) -20.6 to -7.0,  $P < 0.0001$ ,  $I^2 = 80\%$  [8 RCTs, 139 participants]). In trials at low risk of detection bias (i.e., blinded), there was no benefit of SCS compared with sham at less than one month (MD -3.00, 95% CI -9.3 to 3.2,  $I^2 = 0\%$  [2 RCTs, 62 participants]). The authors rated the outcome as very low certainty (Grading of Recommendations, Assessment, Development and Evaluation [GRADE]).

In a single study (Hara 2022), SCS was not superior compared to sham in reducing low back pain at three months (MD -4.0, 95% CI -8.9 to 0.19,  $P = 0.06$ ). The study demonstrated similar results on reducing leg pain intensity (MD -2.0, 95% CI -6.47 to 2.47,  $P = 0.38$ ). The authors rated the outcomes as of moderate certainty (GRADE).

#### Function

In a single study (Hara 2022), SCS was not superior compared to sham in improving function at three months (MD -1.30, 95%CI -3.91 to 1.31,  $P = 0.33$ ).

#### Health-related quality of life

In a single study (Hara 2022), SCS was not superior compared to sham in improving HRQoL at three months (MD 0.04, 95% CI -0.08 to 0.16,  $P = 0.53$ ).

### Spinal cord stimulation plus medical management versus medical management alone

Three unblinded, parallel RCTs that compared SCS plus medical management to medical management alone reported on outcomes at short, medium and long-term follow-up.

#### Pain intensity

Mean back pain intensity was better, though not statistically significant, with the addition of SCS when compared to medical management alone at medium-term follow-up, defined as  $\geq 3$  months to  $< 12$  months (MD -26.0, 95% CI -56.2 to 4.2 points worse,  $I^2 = 98\%$ ,  $P = 0.09$  [3 RCTs, 430 participants]). Mean leg pain intensity was significantly improved with the addition of SCS when compared to medical management alone at medium-term follow-up (MD -18.8, 95% CI -33.2 to -4.5,  $I^2 = 82\%$ ,  $P = 0.01$  [2 RCTs, 290 participants]). The authors rated the outcomes as very low certainty (GRADE).

Participants in the SCS group were 7.4 times more likely to report  $\geq 50\%$  pain reduction compared to the medical management alone group (95% CI 23.4 to 2.3,  $I^2 = 70\%$ ,  $P = 0.0007$  [3 RCTs, 430 participants]) at medium-term follow-up.

At 24-month (long-term) follow-up, a single trial reported a greater number of participants in the SCS group (17/52) achieved  $\geq 50\%$  pain reduction compared with participants in the medical management alone group (8/48), although this difference failed to reach statistical significance (RR 1.96, 95% CI 0.93 to 4.12,  $P = 0.08$ ). These outcomes were rated as very low certainty (GRADE)

### Function

At medium-term follow-up, mean function was better with the addition of SCS compared to medical management alone (MD -16.2, 95% CI -19.4 to -13.0 points better,  $I^2=95%$ ,  $P < 0.00001$  [3 RCTs, 430 participants]) (low certainty).

### Health-related quality of life

It is unclear whether the addition of SCS to medical management has a positive effect on HRQoL compared to medical management alone (MD 7.6, 95% CI 15.8 to -0.6,  $I^2=53%$ ,  $P = 0.07$  [2 RCTs, 289 participants]) at medium-term follow-up<sup>13</sup> (very low certainty).

### Adverse events

At longest follow-up, a larger number of participants in the SCS group (65/157, 41.4%) experienced AEs compared to the medical management alone group (49/179, 27.4%), although this difference is not statistically significant (RR 2.32, 95% CI 0.39 to 13.79,  $I^2= 90%$ ,  $P = 0.35$  [2 RCTs, 336 participants]). A larger number of participants in the SCS group also experienced SAEs (6/65, 9.2%) compared to the medical management group (4/76, 5.3%) at medium-term follow-up (RR 1.73, 95% CI 0.51 to 5.87,  $P = 0.38$  [1 RCT 140 participants]).

Results from one RCT compared withdrawals due to AEs in the high-frequency SCS group (2/83) versus the medical management group (0/76). All adverse event outcomes were rated very low certainty (GRADE).

### Minor outcomes

Three studies reported on medication use at medium-term follow-up. The addition of SCS may reduce opioid use and daily morphine equivalents (MME) in participants. The number of participants using opioids was 15% lower in the SCS group compared to the medical management group (95% CI 27% to 0%,  $I^2=0%$ ,  $P = 0.05$  [3 RCTs, 430 participants]). Daily MMEs were 9.4 points lower in the SCS group compared to the medical management group (95% CI -19.9 to 1.2,  $I^2=0%$ ,  $P = 0.08$  [3 RCTs, 430 participants]). Both outcomes were rated low certainty (GRADE).

## 3.2.2 Included Cochrane review (O'Connell 2021)

O'Connell (2021) evaluated the efficacy, effectiveness, AEs, and cost-effectiveness of SCS for people with chronic pain. The study did not include patients with chronic cancer pain or chronic ischaemic pain. The SR assessed SCS and DRGS by evaluating RCTs that compared:

- active stimulation versus placebo (sham) stimulation
- active stimulation versus usual care or no treatment
- active stimulation plus another intervention versus that intervention alone.

The data were reported on across three different time points – short term (within a month), medium term (three to six months), and long term (at one year or greater than a year) which differed to the Traeger (2023) definitions. The primary outcomes were pain intensity and AEs. Pain intensity was dichotomised where possible with a 30% or greater reduction in pain intensity considered to represent a moderately important benefit, and a 50% or greater reduction in pain intensity considered to represent a substantially important benefit. Secondary outcomes were disability, analgesic medication use, HRQoL, and health economic outcomes. The study characteristics are summarised in Table 7.

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<sup>13</sup> Note: there is an error in Traeger (2023) on page 26 (Figure 9) and page 110 (Analysis 2.7) which show the effect in favour of medical management. The Traeger text regarding this outcome is correct and the effect favours SCS.

**Table 7 Study characteristics of O'Connell (2021)**

Study ID	Search dates	Patient population	Interventions	Comparator	Outcomes	Time points
O'Connell 2021 Cochrane Review	From inception to October 2020 and updated in September 2021	Participants ≥ 18 yrs old with non-cancer and non-ischaeamic pain of >3 mo durations	Any electrical spinal neuromodulation technique that involves the implanting of electrodes in the epidural space around the spinal cord (e.g., SCS and DRGS)	1. Placebo stimulation 2. No treatment 3. Usual care alone (in studies where SCS + another treatment)	<u>Primary:</u> Pain intensity and AEs <u>Secondary:</u> Disability, analgesic medication use, HRQoL, health economic outcomes	Short term: within a mo of implantation Medium term: 4-8 mo post-implantation Long term: >1 yr post-implantation

Abbreviations: AE, adverse event; DRGS, dorsal root ganglion stimulation; HRQoL, health-related quality of life; mo, months; SCS, spinal cord stimulation; yrs, years.

## Included studies

Fifteen published studies with 908 randomised participants met the inclusion criteria (Table 8). Of the 15 RCTs, 11 declared some form of industry funding. Nine of the trials were cross-over studies where study size ranged from 10 to 41 participants. Six trials were parallel studies, study size ranged from 36 to 218 participants.

**Table 8 Characteristics of studies included in O'Connell (2021)**

Study ID	Design	Participants N	Intervention Comparator	Outcomes	Funding Author COIs	Treatment duration
Kemler 2000	Parallel RCT	CRPS 54	SCS (conventional) + Physical therapy Physical therapy	Pain intensity, AEs, HRQoL, costs, costs per QALY	Dutch Health Insurance Council NR	6 mo (up to 5 yrs follow-up)
PROMISE (Rigoard 2019)	Parallel RCT	FBSS 218	SCS (conventional) + OMM OMM	Pain intensity, AEs, HRQoL, disability	Medtronic Yes	Up to 24 mo
PROCESS (Kumar 2007)	Parallel RCT	FBSS 100	SCS (conventional) + CMM CMM	Pain relief, AEs, disability, ODI, HRQoL, Cost	Medtronic Yes	Up to 24 mo
SENZA-PDN (Petersen 2021)	Parallel RCT	PDN 216	SCS (HF) + CMM CMM	Pain intensity, AEs, HRQoL	Nevro Corp. Yes	Up to 24 mo
Slangen 2014	Parallel RCT	PDN 34	SCS (conventional) + BMT BMT	Pain intensity, AEs, HRQoL, medication use	Medtronic Yes	6 mo
de Vos 2014	Parallel RCT	PDN 60	SCS (conventional) + CMM CMM	Pain intensity, AEs, HRQoL, medication use	St Jude Medical Yes	6 mo
Lind 2015	Cross-over RCT	Irritable bowel syndrome 10	SCS (conventional) Sham	Pain intensity, AEs, HRQoL	Medtronic No	6 wks per treatment
Al-Kaisy 2018	Cross-over RCT	FBSS 30	SCS (HF) Sham	Pain intensity, AEs	Medtronic Yes	3 wks per treatment

Study ID	Design	Participants N	Intervention Comparator	Outcomes	Funding Author COIs	Treatment duration
Eldabe 2021	Cross-over RCT	Chronic back pain (SCS responders) 19	SCS (burst) Sham	Pain intensity, AEs, HRQoL	Medtronic Yes	2 wks per treatment
Kriek 2017	Cross-over RCT	CRPS 33	SCS (conventional, HF, burst) Sham	Pain intensity, AEs, medication use, DASH, walking ability, costs	St Jude Medical Yes	2 wks per treatment
Perruchoud 2013	Cross-over RCT	Persistent pain (already receiving SCS) 38	SCS (HF) Sham	Pain intensity, AEs, HRQoL, medication use	Medtronic Yes	2 wks per treatment
Sokal 2020	Cross-over RCT	Chronic pain 18	SCS (conventional, burst, HF) Sham	Pain intensity, AEs, disability, HRQoL, medication use	None Yes	2 wks per treatment
Tjepkema- Cloostermans 2016	Cross-over RCT	Chronic pain (already receiving SCS) 41	SCS (conventional, burst) Sham	Pain intensity, AEs, QoL	None NR	2 wks per treatment
Schu 2014	Cross-over RCT	FBSS (already receiving SCS) 20	SCS (conventional, burst) Sham	Pain intensity, AEs, disability	St Jude Medical Yes	1 wk per treatment
De Ridder 2013	Cross-over RCT	Chronic limb or back pain 15	SCS (conventional, burst) Placebo	Pain intensity	NR Yes	1 wk per treatment

Abbreviations: AE, adverse event; BMT, best medical treatment; CMM, conventional medical management; CRPS, complex regional pain syndrome; DASH, Disabilities of the Arm, Shoulder, and Hand Questionnaire; FBSS, failed back surgery syndrome; HF, high-frequency; HRQoL, health-related quality of life; mo, months; NR, not reported; ODI, Oswestry Disability Index; OMM, optimal medical management; QALY, quality-adjusted life year; QoL, quality of life; PDN, painful diabetic neuropathy; RCT, randomised controlled trial; SCS, spinal cord stimulation; wk(s), weeks; yrs, years.

The SR did not find any eligible RCTs on DRGS. A range of pain conditions were included across the studies. A minimum pain level of at least 4/10 on a visual analogue scale was required for inclusion in the review, although some studies had higher levels. Ten studies stated that pain must be refractory to previous treatment. Four studies included participants who were already implanted with SCS at the time of recruitment.

All of the cross-over RCTs provided data on short-term outcomes only, with the comparator treatment being 'sham'. Of the six parallel trials, all compared SCS plus other management to other management alone; none compared SCS to an alternative treatment.

All of the included outcomes were rated as having an overall high risk of bias by the authors. All parallel studies were open-label with neither participants nor clinicians blinded to the interventions. Blinding in the cross-over, sham stimulation studies was broadly considered suboptimal; furthermore, these studies tended to lack washout periods and to utilise per-protocol type analyses. Most outcomes were subjective and self-reported while information on how AEs were classified or surveyed was poorly reported.

Twenty ongoing studies that evaluated SCS or DRGS were identified in the SR; these are listed in Appendix C.1.1, Table App 5 and Table App 6.

## Findings

### Spinal cord stimulation versus placebo (sham stimulation)

The nine cross-over RCTs that compared SCS with placebo/sham stimulation all reported short-term outcomes only and, as all participants were implanted with SCS devices, they do not provide comparative data on AEs.

There was evidence of a small effect in favour of SCS for reduced pain intensity (MD -8.73, 95% CI -15.67 to -1.78,  $P = 0.005$ ,  $I^2 = 58\%$  [6 RCTs, 164 participants]), which is below the pre-specified threshold for a clinically important effect (MD of 10). The authors rated the outcome as very low certainty (GRADE).

### Spinal cord stimulation plus other intervention versus other intervention

The parallel RCTs that compared SCS plus another intervention (medical management or physical therapy) against that intervention alone were informative at all time points, therefore the medium- and long-term outcomes are reported here.

#### Pain intensity

Results from five RCTs (N=635) provided evidence of a large reduction in pain intensity at medium-term follow-up (MD -31.22, 95% CI -47.34 to -15.10,  $P < 0.001$ ,  $I^2 = 95\%$ ). There was also a significant effect in favour of SCS for the proportion of participants reporting  $\geq 50\%$  pain reduction at medium-term follow-up (RR 7.08, 95% CI 3.40 to 14.71,  $P < 0.001$ ,  $I^2 = 43\%$  [5 RCTs, 597 participants]). The authors rated both outcomes as low certainty (GRADE).

At long-term follow-up, a single RCT (N=44) provided results; there was no clear evidence for an effect on mean difference in pain intensity (MD -7, 95% CI -24.76 to 10.76,  $P = 0.44$ ). A different study (N=87) provided data on the proportion of participants reporting  $\geq 50\%$  pain reduction at long-term follow-up and found a significant effect in favour of SCS (RR 15.15, 95% CI 2.11 to 108.91,  $P = 0.007$ ). Both outcomes were rated as very low certainty (GRADE).

#### Adverse events

AEs were reported variably and with a lack of detail in the included studies. It is likely they are incompletely reported.

The SR estimated that at medium-term follow-up, the risk of lead failure/displacement was 4% (95%CI 4% fewer to 11% more [3 RCTs, 330 participants]), infection was 4.6% (95%CI 1% more to 7% more [4 RCTs, 548 participants]), need for reoperation/reimplantation was 11% (95%CI 2% more to 21% more [4 RCTs, 548 participants]); however, the certainty around these estimates is low or very low.

It was estimated that at long-term follow-up the risk for lead failure/displacement was 55% (95% CI 35% to 75% [1 RCT, 44 participants]) and the risk for reoperation/reimplantation was 94% (95% CI 80% to 107% [1 RCT, 44 participants]), both very low certainty.

The SR identified reports of SAEs in the included studies that were highly likely to be associated with SCS, including “one death resulting from a subdural haematoma following a dural puncture; autonomic neuropathy resulting from a procedure-related infection, prolonged hospitalisation due to a coagulopathy that resulted in procedural complications, an extradural abscess leading to prolonged monoparesis, a case of pulmonary oedema, wound infection, and an incident of device extrusion (O’Connell 2021).”

#### Secondary outcomes

No clear evidence (low to very low certainty evidence) was found to evaluate the effect of SCS on medication use (for example, opioids: RR 0.77, 95% CI 0.58 to 1.01,  $P = 0.06$ ,  $I^2 = 0\%$  [2 RCTs, 154 participants]), or on disability (MD -15.93, 95% CI -35.99 to 4.13,  $P = 0.12$ ,  $I^2 = 92\%$  [2 RCTs, 312 participants]) (very low certainty) at medium-term follow-up.



The SR found positive effects on HRQoL at medium-term follow-up (SMD 0.73, 95% CI 0.46 to 0.99,  $P < 0.001$ ,  $I^2 = 54%$  [5 RCTs, 595 participants]) (low certainty) and no evidence for an effect at long-term follow-up (MD -0.09, 95% CI -0.74 to 0.56 [1 RCT, 44 participants]) (very low certainty evidence).

### 3.2.3 Included systematic review on ischaemic pain (NICE 2008)

The included Cochrane reviews (O’Connell 2021 and Traeger 2023) did not consider patients with ischaemic pain and no SR was identified in the rapid evidence scan to address this indication. This indication was also not discussed in any detail in submissions from sponsors or stakeholders. Nevertheless, the MBS items (Appendix B) refer to ‘pain from refractory angina pectoris’ in some item descriptors.

NICE technology appraisal guidance (TA159) (2008) evaluated the clinical and cost-effectiveness of SCS in the management of chronic pain of neuropathic or ischaemic origin. Although published in 2008, this guidance was considered for review in 2014 and transferred to the ‘static guidance list.’ In the absence of more recent SRs, or studies identified by stakeholders or sponsors, the NICE SR is considered the most comprehensive summary of evidence on the role of SCS in the treatment of ischaemic pain and is included in light of the MBS item descriptors. The NICE evaluation of SCS for pain of neuropathic origin is not reported as it is superseded by the Cochrane reviews (O’Connell 2022; Traeger 2023).

The NICE guidance included RCTs that compared SCS with medical and/or surgical treatment appropriate to the patient’s condition. The patient population of the NICE review (ischaemic pain) is broader than that of the MBS item number (refractory angina). The study characteristics are reported in Table 9.

**Table 9 Study characteristics of NICE (2008)**

Study ID Country	Search dates	Patient population	Interventions	Comparator	Outcomes
NICE 2008 UK	Inception to September 2007	Adults with chronic neuropathic or ischaemic pain who have had an inadequate response to medical or surgical treatment (appropriate to condition) other than spinal cord stimulation	SCS	Medical and/or surgical treatment (appropriate to condition) that does not include SCS	Pain; HRQoL; physical and functional abilities; anxiety and depression; medication use; complications and adverse effects (e.g., procedural complications and technical failures)

Abbreviations: HRQoL, health-related quality of life; SCS, spinal cord stimulation

Note: this review will focus on the findings in the ischaemic pain population therefore the neuropathic population is greyed out

#### Included studies

Eight RCTs that evaluated the effect of SCS on chronic ischaemic pain were included (Table 10). Four RCTs evaluated critical limb ischaemia (CLI) and the remaining four RCTs evaluated angina in coronary artery disease. Pain as a primary outcome was reported in only one of the included studies. The primary outcome in CLI studies were limb salvage rates, whilst in angina studies the primary outcome was either exercise capacity or angina attacks. None of the included trials were blinded.

**Table 10 Characteristics of studies in patients with chronic ischaemic pain included in NICE (2008)**

Study ID N	Participants	Intervention	Comparator	Primary outcome	Follow-up
ESBY trial <sup>a</sup> 104	Angina pectoris	SCS	CABG	Angina attacks	6 & 58 mo
Suy 1994 38	CLI	SCS plus CMM	CMM	Limb salvage rates	24 mo
ESES trial <sup>b</sup> 120	CLI	SCS plus CMM	CMM	Limb salvage rates Pain relief	6, 12, 18 & 24 mo
Jivegard 1995 51	CLI	SCS + peroral analgesics	Peroral analgesics	Limb salvage rates	18 mo

Study ID N	Participants	Intervention	Comparator	Primary outcome	Follow-up
sPiRiT trial <sup>c</sup> 68	Angina pectoris	SCS	Percutaneous myocardial laser revascularisation	Exercise capacity	12 mo
Claeys 1999 <sup>d</sup> 86	CLI	SCS plus PGE1	PGE1	Limb salvage rates	12 mo
DeJongste 1994 17	Angina pectoris	SCS	No SCS	Exercise capacity HRQoL	6-8 wk
Hautvast 1998 25	Angina pectoris	SCS	Inactive stimulator	Exercise capacity	6 wk

Abbreviations: CABG, coronary artery bypass grafting; CLI, critical limb ischaemia; HRQoL, health-related quality of life; mo, months; PGE1, prostaglandin E1; SCS, spinal cord stimulation; wk, weeks.

**a** Associated publications: Ekre 2002; Norrsell 2000; Mannheimer 1998

**b** Associated publications: Spincemaille 2000a (pilot study); Spincemaille 2000b; Klomp 1999; Ubbink 1999; Klomp 1995

**c** Associated publication: McNab 2006

**d** Claeys 1998 is considered the key publication. Associated publications: Claeys 1998; Claeys 1997; Claeys 1996

## Findings

All four trials of CLI (ESES; Suy 1994; Jivegard 1995; Claeys 1998) reported limb survival rates, with no studies reporting a statistically significant difference between groups. Two trials (ESES; Jivegard 1995) reported on pain relief outcomes. Neither trial found a statistically significant difference between groups. The ESES trial also reported on HRQoL and did not find a statistically significant difference between groups.

One angina trial (Hautvast 1998) reported pain outcomes and found no statistically significant difference between SCS and an inactive stimulator. Three trials reported on frequency of angina attacks; two trials found a statistically significant difference in favour of SCS (DeJongste 1994; Hautvast 1998) and one found no statistically significant difference (sPiRiT). Three trials reported on exercise duration or capacity; two trials (DeJongste 1994, Hautvast 1998) reported a statistically significant difference favouring SCS and one reported no difference (sPiRiT). All four trials reported on HRQoL outcomes; three trials found no significant difference between SCS and the comparator while one trial reported a statistically significant difference (DeJongste 1994).

On the basis of these findings, NICE developed the following guidance:

*‘Spinal cord stimulation is not recommended as a treatment option for adults with chronic pain of ischaemic origin except in the context of research as part of a clinical trial. Such research should be designed to generate robust evidence about the benefits of spinal cord stimulation (including pain relief, functional outcomes and quality of life) compared with standard care.’*

An investigator-initiated double-blind, placebo-controlled, cross-over RCT investigating the efficacy of SCS in patients with refractory angina pectoris is expected to complete primary assessments in June 2025 and may provide further evidence for this indication (ClinicalTrials.gov Identifier: NCT04915157) (Vervaat 2023).

### 3.2.4 Additional RCT evidence

Studies comparing one type of SCS with another were excluded from both Cochrane reviews (O’Connell 2021; Traeger 2023). Noting the methodological considerations discussed (Section 3.1.3), RCTs identified by sponsors and stakeholders (Table App 10) and those excluded from the Cochrane reviews (Table App 11, Table App 12), were considered for inclusion to provide additional evidence. Included RCTs needed to report at least medium-term outcomes ( $\geq 3$  months) and to include pain as a primary outcome. The requirement for medium-term outcomes excluded most cross-over designs.

## High-frequency SCS versus conventional SCS

Four studies that compared high-frequency (HF) SCS against conventional SCS were considered applicable: SURF (Bolash 2019), Canós-Verdecho (2021), De Andres (2017) and SENZA-RCT (Kapural 2016) (Table 11). The two largest trials are multicentre, industry-sponsored trials (SURF and SENZA-RCT) which include patients with chronic back or leg pain. The two smaller trials are single site, non-industry funded, both conducted in Spain and include patients with CRPS (Canós-Verdecho 2021) or FBSS (De Andres 2017). The Canós-Verdecho study (2021) is a three-arm trial and includes a comparison to conventional treatment; it was not identified in the O'Connell (2021) Cochrane review, likely due to its publication after the primary search date.

All trials were open-label, with the exception of De Andres (2017), in which patients and investigators were both blinded at study outset. However, due to conventional SCS paraesthesia, which is not experienced with HF-SCS, it is unclear the extent to which blinding was maintained during the study. The study size in Canós-Verdecho (2021) was particularly small given the three arms and there were significant differences in baseline characteristics.

**Table 11** Characteristics of RCT comparing HF-SCS versus conventional SCS

Study ID Design Country	Intervention Comparator	Patient population Follow-up	Outcomes	Funding Author COIs
SURF (Bolash, 2019) Multicentre, open-label RCT (N=99) USA	HF-SCS (10 kHz, Freedom SCS System) SCS (10-1500 Hz [low, burst or moderate frequency according to patient preference], Freedom SCS System)	<u>Population:</u> chronic back or back and leg pain with an average Pain Rating Scale $\geq 5$ (on a 10-point scale) associated with FBSS refractory to CMM for at least 12 mo before enrolment <u>Follow-up:</u> 3 mo (83 patients) & 6 (72 patients) mo	<u>Primary:</u> treatment success ( $\geq 50\%$ reduction in VAS score) <u>Secondary:</u> Changes from baseline in VAS back pain, VAS leg pain ODI EQ-5D-5L AEs	Stimwave Technologies Incorporated Yes
Canós-Verdecho (2021) Single centre, open-label, RCT (N=50) Spain	HF-SCS (10-kHz, Senza system; Nevro Corp) Conventional SCS (RestoreSensor, Intellis MEDTRONIC) Conventional treatment (pharmacological, physical, and blockages)	<u>Population:</u> diagnosed with CRPS with upper limb involvement and with a pain questionnaire (DN4) score $\geq 4$ . Lack of response, defined as no significant patient-reported pain reduction or improved functionality, to CMM and minimally invasive techniques <u>Follow-up:</u> 12 mo (41 patients)	<u>Primary:</u> Pain intensity ( $\geq 50\%$ reduction in VAS score) <u>Secondary:</u> ODI, PD-Q, HAD, SF-12, MOSS AEs	None None
De Andres (2017) Single centre, partially blinded RCT (N=60) Spain	HF-SCS (Senza System, Nevro Corp) Conventional SCS (Surescan RestoreSeonsor, Medtronic)	<u>Population:</u> FBSS, refractory to CMM for $>6$ mo, $\geq 5/10$ on NRS <u>Follow-up:</u> 12 mo (55 patients)	<u>Primary:</u> Pain intensity ( $\geq 50\%$ reduction in VAS score) <u>Secondary:</u> ODI, PD-Q, HAD, SF-12, MOSS, AEs	None None
SENZA-RCT (Kapural 2015; 2016) Multicentre, open-label RCT (N=198) USA	HF-SCS (10 kHz, Senza system; Nevro Corp) Conventional SCS (Precision Plus system; Boston Scientific)	<u>Population:</u> chronic intractable pain of the trunk and/or limbs, refractory to conservative therapy for $\geq 3$ mo, average back pain intensity of $\geq 5/10$ on the VAS; average leg pain intensity of $\geq 5/10$ on the VAS <u>Follow-up:</u> 12 mo (169 patients) and 24 mo (156 patients)	<u>Primary:</u> percentage of subjects who responded to SCS therapy for back pain ( $\geq 50\%$ reduction in VAS score) without a stimulation-related neurological deficit <u>Secondary:</u> leg pain, back pain, ODI	Nevro Corp Yes

Abbreviations: AEs, adverse events; CMM, conventional medical management; COI, conflict of interest; CRPS, complex regional pain syndrome; DN-4, Douleur Neuropathique 4 questions; EQ-5D-5L, EuroQol 5-level version; FBSS, failed back surgery syndrome; HAD, Hospital Anxiety and Depression scale; HF, high-frequency; Hz, hertz; mo, months; MOSS, Medical Outcomes Study Sleep; NRS, numerical rating scale; ODI, Oswestry Disability Index; PD-Q, Pain Detect Questionnaire; RCT, randomised controlled trial; SCS, spinal cord stimulation; SF-12, 12-Item Short Form Survey; VAS, visual analogue scale

## Findings

The outcomes of the trials are presented in Table 12 at medium term (6 months) and long term ( $\geq 12$  months), using the same outcomes reported in the O'Connell (2021) Cochrane review. Analysis was reported as per-protocol across the studies, that is subjects who failed a trial or were lost to follow-up are excluded.

### Pain intensity

Pain was reported on either a 10-point scale (Canós-Verdecho 2021; De Andres 2017; Kapural 2016) or a 100-point scale (Bolash 2019). Although all trials reported significant differences from baseline to follow-up, there were no significant differences between arms, with the exception of the SENZA-RCT which was the largest trial (Kapural 2016).

At 12 months, the SENZA-RCT found a significant mean difference favouring HF-SCS for back pain (MD -1.7, 95% CI -2.6 to -0.8) and leg pain (MD -1.0, 95% CI -2.0 to -0.1). A clinically meaningful difference is 1.0 (O'Connell,2021). There was also a significant difference in favour of HF-SCS for the percentage of patients experiencing more than 50% improvement in pain intensity.

### Adverse events

AEs were poorly reported. Fewer device-related AEs were reported for HF-SCS than conventional SCS in the SURF RCT (Bolash 2019).

### Secondary outcomes

No study reported any significant differences between HF-SCS and conventional SCS for disability or quality of life. The outcomes reported by Canós-Verdecho (2021) are prone to error due to the small sample size and baseline differences.

**Table 12 Outcomes of RCTs comparing HF-SCS versus conventional SCS**

Outcome	Study ID	HF-SCS	Conventional SCS	Summary	Statistical significance
<b>Medium term (6 months)</b>					
Pain intensity (mean change baseline to follow-up) <sup>a</sup>	SURF (Bolash, 2019)	-58.0 $\pm$ 1.0 mm (back)	-49.7 $\pm$ 13.3 mm (back)	MD -8.3 (95% CI Not estimable) (back)	NS
		-41.8 $\pm$ 13.1 mm (leg)	-39.2 $\pm$ 0.3 mm (leg)	MD -2.6 (95% CI Not estimable) (leg)	
	Canós-Verdecho (2021)	-54 (1.3 SEM)	-56 (1.1 SEM)	MD 20 (NR)	NR
	De Andres (2017)	-19.1 (2.09 SD)	-16.7 (2.69 SD)	MD -2.4 (NR)	NS
Pain intensity ( $\geq 50\%$ relief)	SURF (Bolash, 2019)	92% (35/38)	82% (28/34)	10% difference	P= 0.2
Disability (ODI mean change baseline to follow-up)	SURF (Bolash, 2019)	-23 (NR)	-23 (NR)	MD 0 (NR)	NS
	Canós-Verdecho (2021)	-33.8 (NR)	-41.7 (NR)	MD -7.9 (NR)	NR
	De Andres (2017)	-4.08 (SD 60.0)	-5.38 (SD 10.36)	MD -1.3 (NR)	NS
Mean change in HRQoL	SURF (Bolash, 2019)	EQ-5D-L 21.2 (NR)	EQ-5D-L 26.6 (NR)	MD 5.4 (NR)	Non-inferiority test P=0.2, superiority NR
	Canós-Verdecho (2021)	SF-12 345 (NR)	SF-12 365 (NR)	MD 20 (NR)	

Outcome	Study ID	HF-SCS	Conventional SCS	Summary	Statistical significance
Device-related AEs	SURF (Bolash, 2019)	12 AEs in 11 subjects	25 AEs in 15 subjects (1 serious)	-	-
<b>Long term (≥12 months)</b>					
Pain intensity (mean change baseline to follow-up)	Canós-Verdecho (2021)	4.8 (2.0 SEM)	5.6 (1.0 SEM)	MD 0.8 (NR)	NR
	De Andres (2017)	-1.82 (2.45 SD)	-1.44 (2.28 SD)	MD 0.38 (NR)	NS
	SENZA-RCT (Kapural 2016)	-5.0 (SD 2.5) (back) -4.7 (SD 2,8) (leg)	-3.2 (SD 3.0) (back) -3.7 (SD 3.0) (leg)	-1.7 (95% CI: -.26 to -0.8) (back) -1.0 (95% CI: -2.0 to -0.1) (leg)	P<0.001 (back) P=0.03 (leg)
Pain intensity (≥ 50% relief)	SENZA-RCT (Kapural 2016)	76.5% (back)	49.3% (back)	-27.2% (95% CI: 10.1% to 41.8%) (back)	P<0.001 (back)
		72.9% (leg)	49.3% (leg)	-23.6% (95% CI: 5.9% to 38.6%) (leg)	P<0.001 (leg)
Disability (ODI mean change baseline to follow-up)	Canós-Verdecho (2021)	-31.8 (NR)	-41.5 (NR)	MD -9.7 (NR)	NR
	De Andres (2017)	-4.04 (SD 5.77)	-4.14 (SD 8.76)	MD -0.1 (NR)	NS
Mean change in HRQoL	Canós-Verdecho (2021)	SF-12 324 (NR)	SF-12 385 (NR)	MD 61 (NR)	NR

Abbreviations: AEs, adverse events; CI, confidence interval; EQ-5D-5L, EuroQol 5-level version; HF, high-frequency; HRQoL, health-related quality of life; MD, mean difference; NR, not reported; NS, not significant; ODI, Oswestry Disability Index; SD, standard deviation; SCS, spinal cord stimulation; SEM, standard error of the mean; SF-12, 12-Item Short Form Survey  
a normalised to a 0-100 scale for comparison. O'Connell considered a 10-point difference clinically significant (O'Connell, 2021).

## DRGS versus conventional SCS

The included SRs (O'Connell 2021; Traeger 2023) did not identify any studies of DRGS that met their inclusion criteria. The rapid evidence search identified a further five SRs of DRGS; however, all included single arm, pre/post studies and therefore do not provide evidence on the comparative effectiveness of DRGS.

A single RCT on DRGS (Deer 2017) has been published. The ACCURATE study is a parallel, open-label, multicentre RCT in 152 participants comparing DRGS and SCS with follow-up to 12 months (Table 13). The ACCURATE RCT is at high risk of bias due to lack of blinding. The baseline characteristics reported for the patients in the two arms appeared comparable in terms of age, gender, ethnicity and pain-affected region. However, the authors did not report clinical characteristics such as number of previous surgeries, duration of chronic pain, list/number of current pain medications. As such, it was not possible to determine if the patients in each arm were balanced in terms of the severity of their condition or the extent of previous treatment. Although this study does not compare DRGS to either placebo/sham or an alternative (non-neurostimulator) treatment, it is the sole comparative study of these devices identified and therefore the results are reported below.

**Table 13 Characteristics of RCT comparing DRGS versus conventional SCS (Deer 2017)**

Study ID	Intervention Comparator	Inclusion/Exclusion criteria	Outcomes	Funding Author COIs
ACCURATE (Deer 2017) Multicentre, open-label RCT (N=152) USA	DRGS (AXIUM Neurostimulator System) SCS (RestoreUltra or RestoreSensor)	<u>Inclusion:</u> CRPS or causalgia in the lower extremities, naïve to simulation, pain >6 mo, failed ≥2 pharmacological treatments, stable neurologic function, no psychological contraindication <u>Exclusion:</u> changing or escalating pain	<u>Primary:</u> treatment success (composite outcome: ≥50% reduction in VAS score at 3 months and trial end plus no stimulation-related neurological deficit) <u>Secondary:</u> Positional effects on paraesthesia intensity SF-36 Profile of mood states Brief pain inventory Subject satisfaction Stimulation specificity % change in VAS AEs	Spinal Modulation & St Jude Medical Yes

Abbreviations: AE, adverse event; COI, conflict of interest; CRPS, complex regional pain syndrome; DRGS, dorsal root ganglion stimulation; mo, months; N, population; RCT, randomised controlled trial; SCS, spinal cord stimulation; SF-36, 36-item short form survey; VAS, visual analogue scale

## Findings

The outcomes of the trial are presented in Table 14 at medium term (6 months) and long term (12 months), using the same outcomes reported in the O’Connell (2021) Cochrane review. Of the 152 participants randomised, 105 (69%) completed the 12-month visit. For several outcomes, only participants with full data at that time point are included in the analysis.

### Pain intensity

Mean difference in pain intensity favoured DRGS at both medium and long-term follow-up, however insufficient data were provided to assess the significance of this. The minimum clinically important difference is 10 (O’Connell 2021).

At long-term follow-up, the proportion of participants reporting ≥50% pain reduction favoured DRGS (RR 1.4, 95% CI 1.05 to 1.87, p = 0.02).

### Adverse events

Participants receiving DRGS were at greater risk, although not statistically significant, of device-related AEs than those receiving SCS (RR 1.4, 95% CI 0.87 to 1.26, p=0.22) at long-term (12-month) follow-up. The authors attribute this to a longer procedure time and a greater number of implanted leads (3 or 4 compared to 1 or 2) in the DRGS arm. There was no difference in the rate of SAEs. Two SAEs in the SCS arm were infections requiring device explantation.

### Secondary outcomes

HRQoL was measured using the SF-36. No statistically significant difference was found between the DRGS and SCS arms at medium or long-term follow-up.

**Table 14 Outcomes of RCT comparing DRGS versus conventional SCS (Deer 2017)**

Outcomes	Intervention	Comparator	Summary
<b>Medium term (3 or 6 months)</b>			
Pain intensity (mean change baseline to follow-up)	67.5 (SD NR)	56.9 (SD NR)	MD 10.6 (95% CI Not estimable)
Pain intensity (≥ 50% relief in n/N patients (%))	56/69 (81.2%)	39/70 (55.7%)	P < 0.0004

Outcomes	Intervention	Comparator	Summary
SF-36 – physical component, mean score (SD)	11.1 (8.0)	8.6 (8.4)	MD 2.5 (95% CI -0.6 to 5.6)
SF-36 – mental component, mean score (SD)	6.6 (13.2)	4.1 (10.2)	MD 2.5 (95% CI -2.0 to 7.0)
Device-related AEs	NR	NR	-
<b>Long term (12 months)</b>			
Pain intensity (mean change baseline to follow-up)	65.6 (SD NR)	54.2 (SD NR)	MD 11.4 (95% CI Not estimable)
Pain intensity (≥ 50% relief in n/N patients (%))	49/66 (74.2%)	35/66 (53.0%)	P < 0.0004
SF-36 – physical component (mean change baseline to follow-up)	11.5 (9.4)	8.0 (9.0)	MD 3.5 (95% CI -0.1 to 7.1)
SF-36 – mental component (mean change baseline to follow-up)	6.2 (12.3)	3.6 (11.1)	MD 2.6 (95% CI -1.9 to 7.1)
Device related AEs	39 events (28/76 subjects, 37%)	24 events (20/76 subjects, 26%)	RR 1.4 (95% CI 0.87 to 1.26, p=0.22)
Serious AEs	8/76 subjects (11%) 0 SAEs device-related	11/76 subjects (14%) 2 SAEs device-related	RR 0.72 (95% CI 0.31 to 1.71, p=0.62)

Abbreviations: AE, adverse event; CI, confidence interval; ITT, intention to treat; MD, mean difference; NR, not reported; SD, standard deviation; RR, relative risk; SF-36, 36-item short form survey

## Other SCS approaches versus conventional SCS

Four additional RCTs (ESTIMET [Rigoard 2021]; EVOKE [Mekhail 2020]; Fishman (2021) and SUNBURST [Deer 2018]) were identified that compared various modifications to conventional SCS against conventional SCS, have at least moderate follow-up and include pain intensity as an outcome (Table 15). Two of these studies reported that patients and investigators were both blinded (ESTIMET; EVOKE). One study was a cross-over design with patients switching arms after 12 weeks (SUNBURST) and the remainder were parallel arm.

**Table 15** Characteristics of RCTs comparing alternative SCS approaches to conventional SCS

Study ID	Intervention Comparator	Patient population Follow-up	Outcomes	Funding Author COIs
ESTIMET (Rigoard 2021) Multicentre, double-blind RCT (N=115) France	Multicolumn programming of SCS  Conventional SCS	<u>Population:</u> FBSS patients (defined as persistent back and leg pain present for six months following at least one surgical procedure), with pain refractory to well conducted conservative management (with or without drugs) and treated under the guidance of a multidisciplinary pain clinic  <u>Follow-up:</u> 6 mo (100 patients)	<u>Primary:</u> Change in VAS for back pain  <u>Secondary:</u> 50% decrease in VAS ODI EQ-5D-5L AEs	French Ministry of Health  Yes
EVOKE (Mekhail 2020; Mekhail 2022) Multicentre, double-blind RCT (N=134) USA	ECAP-controlled closed-loop SCS (Evoke System, Saluda Medical, Sydney, Australia)  Conventional SCS (Evoke System, Saluda Medical, Sydney, Australia)	<u>Population:</u> chronic, intractable pain of the back and legs (VAS pain ≥60 mm; ODI score 41–80) who were refractory to conservative therapy, on stable pain medications, had no previous experience with spinal cord stimulation, and were appropriate candidates for a spinal cord stimulation trial  <u>Follow-up:</u> 3 mo (125 patients), 12 mo (118 patients)	<u>Primary:</u> Pain intensity (≥50% reduction in VAS score)  <u>Secondary:</u> ODI EQ-5D-5L AEs	Saluda  Yes

Study ID	Intervention Comparator	Patient population Follow-up	Outcomes	Funding Author COIs
Fishman (2021) Multicentre, open-label RCT (N=128) Spain	Differential Target Multiplexed SCS  Conventional SCS	<u>Population:</u> Average back pain intensity $\geq 5.0$ cm on the 10.0 cm VAS with moderate to severe chronic leg pain at the time of enrolment. Stable pain medication regime for at least 30 days prior to enrolment  <u>Follow-up:</u> 3 mo (92 patients), 6 mo (89 patients), 12 mo (79 patients)	<u>Primary:</u> Pain intensity  <u>Secondary:</u> ODI AEs	Stimgenics LLC  Yes
SUNBURST (Deer 2018; D'Souza 2021) Multicentre, open-label cross- over RCT (N=100) USA	Burst SCS (Prodigy™, Abbott, Plano, TX, USA)  Conventional SCS (Prodigy™, Abbott, Plano, TX, USA)	<u>Population:</u> chronic intractable pain of the trunk and/or limbs (VAS $\geq 60$ ), failed $\geq 3$ documented medically supervised treatments as well as treatment with $\geq 2$ classes of medication  <u>Follow-up:</u> 3 mo (96 patients)	<u>Primary:</u> Pain intensity (mean VAS)  <u>Secondary:</u> Pain intensity (responders) ODI AEs	Abbott  Yes

Abbreviations: AEs, adverse events; ECAP, evoked compound action potentials; EQ-5D-5L, EuroQol 5-level version; FBSS, failed back surgery syndrome; mo, months; ODI, Oswestry Disability Index; RCT, randomised controlled trial; SCS, spinal cord stimulation; SF-12, 12-Item Short Form Survey; VAS, visual analogue scale

## Findings

### Pain intensity

Only pain intensity and adverse event rates have been extracted from these trials (Table 16).

The ESTIMET study (Rigoard 2021), which compared multicolumn programming with conventional SCS, did not report any significant differences in pain outcome at medium-term (six month) follow-up.

The EVOKE study (Mekhail 2020), which compared a closed-loop system with conventional SCS, reported a significant difference in favour of the closed-loop system in a responder analysis at both medium and long-term follow-up. Mean change in pain intensity also significantly favoured the closed-loop system at both medium and long-term follow-up, with the difference around the threshold for clinical significance. The results were sustained at 24-month follow-up (Mekhail, 2022; not shown in Table 16).

Fishman (2021) compared differential targeted multiplex SCS with conventional SCS. A statistically significant difference in favour of the intervention was reported in responder analysis for back pain at medium and long-term follow-up. For leg pain, the statistical significance was not reported and the difference between groups was less. Mean change was non-inferior for back pain at medium-term follow-up, with a similar difference at long-term follow-up. The mean difference was less for leg pain.

SUNBURST (Deer 2018) compared burst SCS with conventional SCS. A responder analysis (defined as  $\geq 30\%$  pain relief) was undertaken, but mean pain intensity values were not reported. The mean difference between arms at medium-term follow-up was statistically significant, although the values were similar to those reported by ESTIMET and do not meet criteria for clinical significance (O'Connell 2021).

All studies demonstrated significant improvements in both arms from baseline to follow-up in pain outcomes. Although ESTIMET and EVOKE were blinded with respect to the type of SCS, the study is unblinded with respect to SCS treatment itself.

### Adverse events

AEs were often pooled across study arms. In those that reported device-related AEs by trial arm, rates were similar.



**Table 16 Outcomes of RCTs comparing alternative SCS approaches to conventional SCS**

Outcome	Study ID	Intervention	Conventional SCS	Summary	Statistical significance
<b>Medium term (≥3 months)</b>					
Pain intensity (mean change baseline to follow-up) <sup>a</sup>	ESTIMET	31.7 (95% CI: 23.2 to 40.3) (back) 49.2 (95% CI: 41.7 to 56.6) (leg)	26.2 (95% CI: 17.9 to 34.5) (back) 44.0 (95% CI: 35.6 to 52.4) (leg)	MD 5.5 (NR) (back) MD 5.2 (NR) (leg)	P=0.3 (back) P=0.3 (leg)
	EVOKE	59.8 (SD 23.5)	49.2 (SD 30.2)	MD 10.6 (95% CI: 1.0-20.2)	P=0.03
	Fishman (2021)	53.6 (SD 26.3) (back) 52.9 (SD 24.1) (leg)	33.7 (SD 25.2) (back) 47.6 (SD 25.2) (leg)	MD 19.9 (NR) (back) MD 5.3 (NR) (leg)	Non-inferior (back) NR (leg)
	SUNBURST	NR	NR	MD 5.1 (NR)	P<0.017
Pain intensity (≥ 50% relief)	ESTIMET	46.9% (23/49) (back) 71.4% (35/49) (leg)	39.2% (20/51) (back) 62.7% (32/51) (leg)	14.9% difference (back) 8.7% difference (leg)	P= 0.5 (back) P=0.4 (leg)
	EVOKE	82% (51/62)	60% (38/63)	21.9% (95% CI: 6.6 to 37.3)	P=0.0052
	Fishman (2021)	80.1% (90% CI: 70.6%–89.7%) (back) 77.1% (NR) (leg)	51.2% (90% CI: 40.0%–62.4%) (back) 72.5% (NR) (leg)	28.9% (NR) (back) 4.6% (NR) (leg)	p < 0.0001 (back) NR (leg)
<b>Long term (≥12 months)</b>					
Pain intensity (mean change baseline to follow-up)	EVOKE	58.1 (SD 23.6)	46.4 (SD 32.3)	MD 11.7 (95% CI: 1.4-22.0)	P=0.03
	Fishman (2021)	54.8 (SD 26.9) (back) 55.3 (SD 27.9) (leg)	36.2 (SD 25.3) (back) 49.5 (SD 23.8) (leg)	MD 18.6 (NR) (back) MD 5.8 (NR) (leg)	NR (back) NR (leg)
Pain intensity (≥ 50% relief)	EVOKE	83% (49/59)	61% (36/59)	22.0% (95% CI: 6.3 to 37.7)	P=0.0060
	Fishman (2021)	83.7% (NR) (back) 80.0% (NR) (leg)	51.1% (NR) (back) 75.0% (NR) (leg)	32.6% (NR) (back) 5.0% (NR) (leg)	Significant (value NR) (back) NR (leg)
Device-related AEs	EVOKE	23 AEs in 13 patients (19% [95% CI: 10.8–30.9])	11 AEs in 11 patients (16% [95% CI: 8.5–27.5])	-	-
	Fishman (2021)	4 AEs in 4 patients (6%)	8 AEs in 7 patients (11.5%)	-	-

Abbreviations: AE, adverse event; CI, confidence interval; MD, mean difference; NR, not reported; SCS, spinal cord stimulation; SD, standard deviation

a. normalised to a 0-100 scale for comparison. O’Connell considered a 10 point difference clinically significant (O’Connell, 2021).

### 3.2.5 Additional non-randomised comparative evidence

As SCS is a long-term implanted device, appropriately adjusted non-randomised comparative studies may provide additional information to inform the assessment of comparative effectiveness, possibly overcoming some of the limitations of RCTs. These studies were identified from sponsor and stakeholder submissions.

From the 255 studies identified for this report (see Section C.1.2), a total of five are non-randomised comparative cohort studies. Two are large registry studies (Dhruva 2023 and Vu 2022) and three are

multicentre studies (Brill 2022; De Ridder 2015; Veizi 2017)<sup>14</sup>. These multi-institution studies provide little additional value in light of the available RCT evidence and are not considered further.

## Registry studies

The Dhruva 2023 registry study (Table 17) used data from the Optum Labs Data Warehouse in the USA and included patients with back and extremity pain of various aetiology. Patients who received SCS were compared with those who instead received (CMM): pharmacological; non-pharmacological; or surgical interventions. Confounding was addressed with propensity score matching that drew on an extensive range of variables. Cohorts were paired 1:5 (SCS vs no SCS).

The primary outcomes were two pain surrogates:

- chronic opioid use (greater than or equal to 120 days' supply, or 10 or more fills)
- epidural and facet corticosteroid injection use.

Safety outcomes were captured for patients in the SCS group. They included lead/generator breakdown, displacement, infection or inflammation, and other mechanical complications which were separately analysed. Revisions and removals were also analysed separately: lead/generator revision; lead removal; and generator removal.

Follow-up periods were the first year and the second year after index date.

The Vu 2022 registry study (Table 17) used the TriNetX Diamond Network and was restricted to patients with post-laminectomy syndrome (PLS). Two propensity score matched cohorts were defined – SCS or no SCS. Two opioid use outcomes were reported: cessation of, or commencement of, long-term opioid therapy in the 12-month study periods (from 3 to 15 months post-SCS implantation or post-PLS index date).

**Table 17** Characteristics of large, propensity matched comparative studies identified from stakeholder submissions

Study ID	Title	Population and setting	Comparison, outcomes and follow-up
<b>Registry studies</b>			
Dhruva 2023	Long-term Outcomes in Use of Opioids, Nonpharmacologic Pain Interventions, and Total Costs of Spinal Cord Stimulators Compared With Conventional Medical Therapy for Chronic Pain	Patients with FBSS, CRPS, chronic pain syndrome, and other chronic post-surgical back and extremity pain  Optum Labs Data Warehouse, Oct 2015 to Aug 2020	SCS (n=1,260) vs CMM (n=6,300) in propensity score matched sets (1:5) selected from original cohorts of 1,419 (SCS) and 91,307 (no SCS)  Outcomes: <ul style="list-style-type: none"> <li>• chronic opioid use<sup>a</sup>;</li> <li>• epidural and facet corticosteroid injection use;</li> <li>• other treatments, incl new spine surgery<sup>b</sup>;</li> <li>• healthcare utilisation and costs;</li> <li>• complications.</li> </ul> Time points: 12 & 24 months (min follow-up 12 months)
Vu 2022	Association of Spinal Cord Stimulator Implantation with Persistent Opioid Use in Patients with Post-laminectomy Syndrome	Patients with PLS  TriNetX Diamond database, May-Aug 2021	Any SCS modality (n=17,334) vs no SCS (n=173,328) Propensity score matched sets (1:10) <sup>c</sup> selected from original cohorts of 26,179 (SCS) and 526,758 (no SCS)  Cessation of, or prevention of initiating, long-term opioid use, defined as $\geq 6$ scripts within 12-month follow-up period (3-15 months after implantation/index date)

<sup>14</sup> A conference abstract for a comparative study was supplied by stakeholders for the use of antibacterial envelopes but is not included here as it does not compare SCS with no SCS or an alternative modality of SCS (Persad 2022).

Abbreviations: CMM, conventional medical management; CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; PLS, post-laminectomy syndrome; SCS, spinal cord stimulation; vs, versus

**a** Defined as total length of opioid possession of 90 days or longer with either (1) greater than or equal to 120 days' supply or (2) 10 or more fills  
**b** Included long-acting opioid use; greater than 50 morphine milligram equivalent (MME) per day; radiofrequency ablations; new spine surgeries; and any fills for non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, antidepressants, gabapentinoids, and benzodiazepines  
**c** See supplemental material for results for propensity matched sets

## Findings

Dhruva (2023) reported that during the first 12 months, patients with SCS were more likely to have chronic opioid use, long-acting opioid use and >50 morphine milligram equivalent (MME)/day. During the second year, there were no statistically significant differences in these pharmacologic pain treatments between the SCS and CMM groups. For those patients taking opioids prior to the index date, there was no difference in discontinuation rates between the SCS and CMM groups. SCS patients were less likely to receive epidural and facet corticosteroid injections in the first year, but not the second.

During the entire follow-up period, 22.1% of patients in the SCS group had an implant removal and/or revision; 10% of these were in the absence of a complication, which the authors infer was due to a lack of effectiveness.

The authors concluded that SCS “was not associated with a reduction in opioid use or non-pharmacologic pain interventions at 2 years. SCS was associated with higher costs, and SCS-related complications were common.” They also note the study limitations, including potential residual confounding (although 65 variables were used in propensity score matching) and the use of surrogate outcomes for pain. However, this large registry study presents the best currently available ‘real-world’ observational evidence for SCS.

Vu (2022) reported that SCS was associated with a small reduction in opioid scripts, and with a small decrease in the likelihood of commencing opioid therapy. These findings were observed when a threshold of  $\geq 6$  scripts per 12 months was used, but the associations were lost when the threshold was reduced to  $\geq 4$  scripts per 12 months. The authors concluded that ‘these findings suggest that under real-life conditions, SCS was associated with small, clinically questionable associations with opioid discontinuation and not starting opioids in the context of PLS.’

### 3.2.6 Non-comparative evidence

As discussed in Section 1.2.1, this PLR was triggered by an Australian article by Jones et al (2022), which provided an analysis of SCS-attributed AEs reported to the TGA between July 2012 and January 2019. Data from the Australian Institute of Health and Welfare’s (AIHW) National Hospital Morbidity Database was used to provide context to the analysis, by providing information on the number of SCS implanted and retrieved per year in Australia. This methodology has been criticised (Sullivan 2023 and stakeholder submissions). Although the review provides useful information on safety signals, it is not a robust methodology for understanding long-term AE rates associated with SCS.

Sponsor and stakeholder submissions provided additional references to support the long-term safety of SCS (see Table App 13 for non-comparative studies and Table App 15 for safety studies). As the focus of this PLR is on comparative clinical effectiveness, these studies have been collated in Appendix C.1.2 of this report but have not been evaluated.

# 4 Comparative cost-effectiveness

The research question to focus the review is:

*What evidence is available on the comparative cost-effectiveness of SCS for the treatment of chronic pain compared to standard care or other therapeutic approaches? Can any conclusions be drawn from the evidence base?*

## 4.1 Methodology

The research question was addressed by undertaking a literature review of existing comparative cost-effectiveness studies and synthesising this with any additional economic evidence provided by DoHAC, sponsors and stakeholders.

The literature search was undertaken to identify published SRs and primary studies of comparative economic evaluations that focus on SCS and DRGS. The economic evaluations included for assessment were cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses. Published studies and sponsor/stakeholder submissions that included only cost analyses were not included in this evaluation.

Some economic studies that were returned in the literature search treated CMM as background therapy to which SCS was introduced as an add-on; these have been treated as eligible as the definition between studies of CMM was in any case variable.

Further details of the methodology are provided in Appendix C.2.

## 4.2 Summary of the evidence

A total of three publications were included in this review of SCS cost-effectiveness: a recent, comprehensive SR of published economic evaluations by Niyomsri (2020), a primary study subsequently published by Rojo (2021), and an Australian economic evaluation provided by DoHAC (Deloitte 2019) Two further studies initially appeared to be eligible for inclusion but were excluded:

- Patel (2022) was excluded due to cross-over prior to the primary endpoint
- Mekhail (2021) was excluded given the comparison with CMM was based on pre-treatment values and was not a legitimate study treatment group.

Rationale for included and excluded studies is provided in Appendix C.2.2 Included studies.

### 4.2.1 Cost-effectiveness studies from other countries

Niyomsri (2020) assessed economic evaluations of SCS and DRGS for the management of a number of chronic pain conditions and included published studies that incorporated cost-effectiveness, cost-utility or cost-benefit analyses. The study characteristics are summarised in Table 18.

**Table 18 Study characteristics of systematic review (Niyomsri 2020)**

Study ID	Search dates	Patient population	Interventions	Comparator	Outcomes
Niyomsri 2020	Inception to July 12, 2019 K=14	Patients with chronic pain	SCS or DRGS	Any alternative therapy	Costs Clinical or utility outcomes ICER

Abbreviations: DRGS, dorsal root ganglion stimulator, ICER, incremental cost-effectiveness ratio; SCS, spinal cord stimulation; UK, United Kingdom; USA, United States of America.

## Included studies

Fourteen studies judged to be of acceptable quality were included in the SR; all assessed SCS and considered chronic pain as a result of refractory angina pectoris, FBSS, CRPS, diabetic peripheral neuropathy (DPN), or peripheral arterial disease (Table 19). Six of the included studies were model based, and ten adopted a healthcare perspective. All models were from North America or Europe; none were conducted in Australia.

One additional study that was published after the Niyomsri (2020) SR was identified in the literature review for this PLR. This study (Rojo 2021) is also shown in the table below.

**Table 19** Characteristics of cost-effectiveness studies from other countries

Study ID Country	Perspective Time horizon EE type	Participants	Intervention Comparator	Funding Author COIs
Andrell 2003 Sweden	Health care 2 yrs CEA (informal) <sup>a</sup> ; trial based	Severe angina pectoris	SCS CABG	University of Goteborg & Swedish Heart Lung Foundation & Swedish Society of Medicine NR
Annemans 2014 UK	Health care 15 yrs CUA; model based	FBSS	HF10 SCS CMM; reoperation	NR NR
Dyer 2008 UK	Health care 2 yrs CUA; model based	Refractory angina pectoris	SCS PMR	Medtronic No
Hollingworth 2011 USA	Workers' compensation (medical & productivity loss) 2 yrs CEA; effectiveness data from case series only	FBSS	Trial SCS PC evaluation; usual care	NR No
Kemler 2002 NL	Societal 1 yr, lifetime CUA; trial based	Chronic RSD	SCS + PT PT	Dutch Health Insurance Council No
Kemler 2010 UK	Health care 15 yrs CUA; model based	CRPS type I	SCS + CMM CMM	Medtronic NR
Klomp 2006 NL	Societal 2 yrs CEA (informal) <sup>a</sup> ; trial based	CLI	SCS BMT	Dutch Fund for Investigative Medicine No
Kumar 2002 Canada	Health care 5 yrs CEA (informal) <sup>a</sup> ; trial based (case series)	Chronic pain	SCS BMT	No No
Kumar 2013 Canada	Health care 20 yrs CUA; model based	FBSS; CRPS; PAD; RAP	SCS + CMM CMM	Mitacs Medtronic; Boston Scientific
North 2007 USA	Health care 3 yrs CUA; trial based	FBSS	SCS reoperation	Medtronic NR
Rojo 2021 Spain	Health care 5 yrs CUA; trial based	FBSS	SCS + CMM CMM	NR Member of Axentiva Solutions (consulting/ advisory services group) Boston Scientific
Simpson 2009 UK		FBSS; CRPS	SCS + CMM CMM	National Institute of Health (UK) HTA

Study ID Country	Perspective Time horizon EE type	Participants	Intervention Comparator	Funding Author COIs
	Health care 15 yrs CUA; model based	FBSS	SCS + CMM reoperation	Programme No
Slangen 2017 NL	Societal; health care 1 yr CUA; trial based	PDPN	SCS + BMT BMT	Medtronic No
Taylor 2005 UK	Health care 2 yrs; lifetime CUA; model based	FBSS	SCS CMM	Medtronic NR
Taylor 2010 UK	Health care 15 yrs CUA; model based	NR FBSS	SCS CMM; reoperation	Medtronic Medtronic

Source: Studies identified in Niyomsri (2020) systematic review, and Rojo (2021)

Abbreviations: BMT, best medical treatment; CABG, coronary artery bypass graft surgery; CEA, cost-effectiveness analysis; CLI, chronic limb ischaemia; CMM, conventional medical management; CRPS, complex regional pain syndrome; CUA, cost-utility analysis; FBSS, failed back surgery syndrome; HF 10, high-frequency (10kHz); HTA, health technology assessment; NL, The Netherlands; NR, not reported; PAD, peripheral arterial disease; PC, pain clinic; PCI, percutaneous coronary intervention; PDPN; painful diabetic polyneuropathy; PMR, percutaneous myocardial laser revascularisation; PT, physical therapy; RAP, refractory angina pectoris; RSD, reflex sympathetic dystrophy; SCS, spinal cord stimulation; UK, United Kingdom.

a Separate cost and effectiveness analyses; an ICER was not calculated.

## Findings

The results of the cost-effectiveness studies as reported by Niyomsri (2020) are presented in Table 20, together with the recent cost-effectiveness study by Rojo (2021).

The findings demonstrate that although initial costs of SCS devices are high, studies with longer-term time horizons tend to report that SCS is cost effective as the modelled improvement in health outcomes is extrapolated over this timeframe. The authors note that the models were limited by a lack of long-term clinical data and missing follow-up costs.

**Table 20 Outcomes of cost-effectiveness studies from other countries**

Study ID Country	Time horizon Perspective Participants	ICER as reported by study	ICER as reported by Niyomsri (2019 GBP)	Conclusion
<b>Long-term horizon</b>				
Annemans 2014 UK	15 yrs Health care FBSS	<u>HF-SCS vs. CMM</u> : £3,153/QALY <u>HF-SCS vs. reoperation</u> : £2,666/QALY	<u>HF-SCS vs. CMM</u> : £3,428/QALY <u>HF-SCS vs. reoperation</u> : £2,898/QALY	SCS cost effective
Kemler 2002 NL	Lifetime Societal Chronic RSD	<u>SCS + PT vs. PT</u> : Dominant	<u>SCS + PT vs. PT</u> : Dominant	SCS cost saving
Kemler 2010 UK	15 yrs Health care CRPS type I	<u>SCS + CMM vs. CMM</u> : £3,562/QALY	<u>SCS + CMM vs. CMM</u> : £4,285/QALY	SCS cost effective
Kumar 2013 Canada	20 yrs Health care FBSS; CRPS; PAD; RAP	<u>SCS + CMM vs. CMM</u> : <u>FBSS</u> : \$9,293/QALY <u>CRPS</u> : \$11,216/QALY <u>PAD</u> : \$9,319/QALY <u>RAP</u> : \$9,984/QALY	<u>SCS + CMM vs. CMM</u> : <u>FBSS</u> : £5,906/QALY <u>CRPS</u> : £7,128/QALY <u>PAD</u> : £5,922/QALY <u>RAP</u> : £6,345/QALY	SCS cost effective
Simpson 2009 <sup>a</sup> UK	15 yrs Health care FBSS; CRPS	<u>FBSS</u> <u>SCS + CMM vs. CMM</u> : £7,996/QALY <u>SCS + CMM vs. reoperation</u> : £7,043/QALY	<u>FBSS</u> <u>SCS + CMM vs. CMM</u> : £9,892/QALY <u>SCS + CMM vs. reoperation</u> : £8,713/QALY	SCS cost effective

Study ID Country	Time horizon Perspective Participants	ICER as reported by study	ICER as reported by Niyomsri (2019 GBP)	Conclusion
		<u>CRPS</u> SCS + CMM vs. CMM: £25,095/QALY	<u>CRPS</u> SCS + CMM vs. CMM: £31,046/QALY	
Taylor 2005 UK	Lifetime Health care FBSS	<u>SCS vs. CMM</u> : Dominant	<u>SCS vs. CMM</u> : Dominant	SCS cost saving
Taylor 2010 UK	15 yrs Health care FBSS	<u>SCS vs. CMM</u> : £5,624/QALY <u>SCS vs. reoperation</u> : £6,392/QALY	<u>SCS vs. CMM</u> : £6,958/QALY <u>SCS vs. reoperation</u> : £7,908/QALY	SCS cost effective
<b>Medium-term horizon</b>				
Kumar 2002 Canada	5 yrs Health care Chronic pain	<u>SCS vs. BMT</u> : Dominant	<u>SCS vs. BMT</u> : Dominant	SCS cost saving
Rojo 2021 Spain	5 yrs Health care FBSS	<u>SCS + CMM vs. CMM</u> : €27,330/QALY	NA	SCS cost effective
<b>Short-term horizon</b>				
Andrell 2003 Sweden	2 yrs Health care Severe AP	<u>SCS vs. CABG</u> : NR	<u>SCS vs. CABG</u> : dominant	SCS cost saving
Dyer 2008 UK	2 yrs Health care Refractory AP	<u>SCS vs. PMR</u> : £46,000/QALY	<u>SCS vs. PMR</u> : £58,356/QALY	SCS not cost effective
Hollingworth 2011 USA	2 yrs Workers' compensation FBSS	<u>SCS vs. usual care</u> : \$334,704/successful outcome <sup>b</sup> <u>SCS vs. PC</u> : \$131,146/successful outcome <sup>b</sup>	<u>SCS vs. usual care</u> : £283,788/successful outcome <sup>b</sup> <u>SCS vs. PC</u> : £111,196/successful outcome <sup>b</sup>	SCS not cost effective
Kemler 2002 NL	1 yr Societal Chronic RSD	<u>SCS + PT vs. PT</u> : €22,582/QALY	<u>SCS + PT vs. PT</u> : £28,128/QALY	SCS cost effective
Klomp 2006 NL	2 yrs Societal CLI	<u>SCS vs. BMT</u> : NR	<u>SCS vs. BMT</u> : NR	SCS not cost effective
North 2007 USA	3 yrs Health care FBSS	<u>SCS vs. reoperation</u> : NR	<u>SCS vs. reoperation</u> : Dominant	SCS cost saving
Slangen 2017 NL	1 yr Societal; health care PDPN	<u>Societal perspective</u> <u>SCS + BMT vs. BMT</u> : €94,160/QALY <u>Health care perspective</u> <u>SCS + BMT vs. BMT</u> : €34,519/ successfully treated patient <sup>c</sup>	<u>Societal perspective</u> <u>SCS + BMT vs. BMT</u> : £89,173/QALY <u>Health care perspective</u> <u>SCS + BMT vs. BMT</u> : £32,691/ successfully treated patient <sup>c</sup>	SCS not cost effective
Taylor 2005 UK	2 yrs Health care FBSS	<u>SCS vs. CMM</u> : €45,819/QALY	<u>SCS vs. CMM</u> : £49,151/QALY	SCS not cost effective

Abbreviations: AP, angina pectoris; BMT, best medical treatment; CI, confidence interval; CLI, chronic limb ischaemia; CMM, conventional medical management; CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; HF, high-frequency; NA, not applicable; NL, The Netherlands; NR, not reported; PAD, peripheral arterial disease; PC, pain clinic; PDPN, painful diabetic polyneuropathy; PMR, percutaneous

myocardial laser revascularisation; PT, physical therapy; RAP, refractory angina pectoris; RSD, reflex sympathetic dystrophy; SCS, spinal cord stimulation; UK, United Kingdom; USA, United States of America.

Note: 'Dominant' indicates that the intervention saves money and is more effective/improves wellbeing.

a. Results refer to independent economic assessment performed by the School of Health and Related Research (SchARR).

b. Cost per additional patient who meets the primary success criterion ( $\geq 50\%$  reduction in leg pain, a two-point or greater improvement on the Roland Disability Questionnaire (RDQ), and less than daily opioid medication use).

c. Cost per successfully treated patient defined as  $\geq 50\%$  relief of pain intensity on a weighted numeric rating scale, for 4 days during daytime or night-time, or a score of  $\geq 6$  on a 7-point Likert scale (6=much improved; 7=very much improved) of the Patient Global Impression of Change scale for pain and sleep at 12 months.

## 4.2.2 Cost-effectiveness studies from Australia

Deloitte Access Economics was contracted by the Neuromodulation Society of Australia and New Zealand (NSANZ), PainAustralia and the Faculty of Pain Medicine, Australia and New Zealand College of Anaesthetists, to undertake a report on the cost-effectiveness of pain devices (SCS and intrathecal pumps). Deloitte (2019) evaluated the cost-effectiveness of SCS versus usual care based on the probability of optimal pain relief (defined as achievement of a 50% or greater reduction in pain from the baseline level, using a visual analogue scale [VAS]).

A Markov model was used to compare treatments in FBSS and CRPS patients. (The study also evaluated intrathecal pumps for the treatment of cancer pain; however, this is not within scope of this review). The study characteristics of Deloitte (2019) are summarised in Table 21.

**Table 21 Study characteristics of Deloitte (2019)**

Study ID Country	Objective/ research question	Perspective Time horizon EE type	Population	Intervention Comparator	Source of effectiveness inputs	Funding Author COIs
Deloitte 2019 Australia	Identify the benefits that pain devices (SCS and intrathecal pumps) can provide, and their associated cost-effectiveness	1. Health system; 2. Societal 15 yrs CUA; model based	FBSS; CRPS	SCS <u>FBSS</u> : UC + reoperation <u>CRPS</u> : UC including inpatient ketamine infusions	Selected RCT and observational studies Expert opinion	NSANZ NR

Abbreviations: COI, conflict of interest; CRPS, complex regional pain syndrome; EE, economic evaluation; FBSS, failed back surgery syndrome; NSANZ, Neuromodulation Society of Australia and New Zealand; SCS, spinal cord stimulation; UC, usual care.

The Deloitte model employed a similar approach to that presented in the economic evaluation commissioned for the UK's National Institute for Health Research (NIHR) HTA Program (Simpson 2009), including a 12-month cycle length with three health states: optimal pain relief, suboptimal pain relief and death. The model had a decision analytic structure for the first 6 months, followed by a Markov process for up to 15 years, depending on patient characteristics. A 5% discount rate was used.

Usual care was assumed to involve a repeat spinal fusion in FBSS patients (5% per annum), and quarterly inpatient ketamine infusions in a proportion of CRPS type I patients (20%; the authors acknowledged that this does not necessarily represent standard care for all patients).

The model assumed that the probability of a successful trial of SCS was 82.7%, taken from the open-label PROCESS trial (Kumar 2005). Similar to Simpson (2009), the probability of device-related complications was assumed to be 18% per annum (after the initial 6 months). The probability of a patient achieving an optimal health state after undergoing SCS implantation was 58.5%, which was based on the PROCESS trial (Kumar 2007). Annual transition probabilities were based on Simpson (2009) and updated in consultation with NSANZ.

Utility values for optimal and suboptimal pain relief were taken from the cost-effectiveness analysis by Kumar (2013), based on EQ-5D scores at baseline and 6 months from a Canadian cohort of patients with FBSS (N=233) or CRPS (N=53) who received SCS or CMM.



Complications were not modelled as separate health states because of the relatively short amount of time that patients would spend in those states. The Deloitte model differed from that of Simpson (2009) in the approach used to capture device-related complications. Deloitte incorporated the cost of complications as a component of the ongoing cost of SCS treatment but held the health utility constant across the year, whereas Simpson (2009) assumed different utility values and health system costs for patients with and without complications.

Health system cost inputs included the cost of trial stimulation, the implantation procedure and explantation. These costs were identical for FBSS and CRPS patients. Ongoing maintenance costs were also incorporated in the model, with higher costs for CRPS than FBSS, primarily due to the cost of regular inpatient ketamine infusions (applied to 2% of patients with a SCS and 20% of patients without). The model assumed that total medication costs (opioids) were reduced by 25% at one year after SCS, based on an observational study of United States insurance claims data by Sharan (2018). More recent propensity matched observational studies have found little difference in opioid use (see Section 3.2.5 Additional non-randomised comparative evidence).

The authors presented a societal perspective as an additional analysis incorporating lost productivity in the model. This perspective has not been considered here as this PLR is focused on implications to the PL and associated Government health budgets.

The Deloitte economic evaluation was undertaken on behalf of, and funded by, the SCS stakeholders peak body in Australia.

## Findings

The findings of the cost-effectiveness analysis, from the perspective of the health system, are presented in Table 22.

**Table 22 Outcomes of Deloitte (2019) – health care perspective**

Study ID	Incremental costs (\$AUD)	Incremental effectiveness (QALY)	ICER (\$AUD/QALY)	Sensitivity analysis	Conclusion
Deloitte 2019 Australia	FBSS: \$958 CRPS: \$188	FBSS: 0.06 CRPS: 0.08	FBSS: \$15,070 CRPS: \$2,321	Model sensitive to time horizon, discount rate, ongoing costs of SCS/UC treatment, device longevity	SCS cost effective

Abbreviations: \$AUD, Australian dollars; CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; ICER, incremental cost-effectiveness ratio; SCS, spinal cord stimulation; QALY, quality-adjusted life year; UC, usual care.

Cost increments for FBSS and CRPS were quite different, at \$958 and \$188 respectively, likely reflecting the higher ongoing maintenance costs for CRPS patients in the usual care arm, due to the assumptions about inpatient ketamine infusions.

The model showed that each SCS patient gained 0.06 and 0.08 QALYs per year when compared to usual care for the treatment of FBSS and CRPS, respectively. The authors commented that the utility gained for patients receiving SCS was higher than in the usual care arm in both optimal and suboptimal health states due to the maintenance of pain relief with SCS, while the treatment effect of alternative therapies generally wears off over time.

From a health system perspective, SCS devices were considered cost effective in the treatment of FBSS and CRPS (type I) when compared to usual care. The incremental cost-effectiveness ratio (ICER) was \$15,070 per QALY gained for patients with FBSS and \$2,321 per QALY gained for patients with CRPS.

Univariate sensitivity analyses indicated that the model was most sensitive to the time horizon, discount rate, ongoing costs of treatment in the SCS arm, and device longevity. When the model time horizon was reduced from 15 to 2 years, the ICER increased to \$97,986 per QALY for FBSS patients and \$73,833 per

QALY for CRPS patients, reflecting the high up-front costs of the intervention. When ongoing costs in the SCS arm were increased by 20% (which could be expected if the assumed reductions in opioid use were not realised in practice), the ICER increased to \$22,804 per QALY for FBSS and \$8,758 per QALY for CRPS. When the device life span was reduced from nine to five years, the model indicated the cost is over four times greater for treatment of FBSS (\$2,861) and 11 times greater for treatment of CRPS (\$2,095), resulting in ICERs of \$45,017 per QALY for FBSS and \$25,869 per QALY for CRPS. The authors' base case assumption that the device life span was 8-10 years may not be plausible in practice.

The report presented a reasonably detailed breakdown of cost inputs from the Australian health care perspective; however, it is unclear whether the analysis adequately incorporated revision surgeries, and lead and device replacements over the longer term, given the lack of reliable clinical studies reporting long-term outcomes.

Lastly, the clinical evidence underpinning the analysis is based on studies at high risk of bias due to lack of blinding, with inadequate follow-up for a device that is permanently implanted. The treatment effect modelled over the 15-year time horizon is not supported by reliable long-term clinical data. The model assumes that the treatment effect (pain relief and HRQoL benefits) is maintained over time; the potential for a waning in pain relief is not captured in the base case or sensitivity analyses.

# 5 Patient selection and management

The research question to focus the review is:

*What evidence-based clinical practice guidelines are available for patient selection and management of spinal cord stimulation? If key guidelines are identified, what recommendations do they make?*

## 5.1 Methodology

A grey literature search was conducted to obtain relevant clinical practice guidelines, HTAs, position statements, and regulatory advice. Additional evidence was also extracted from the feedback received from the sponsors and stakeholders. Due to the volume of relevant publications, a restriction to evidence published in the last ten years was applied. A total of 13 publications were included in the current review, including multiple publications from the Neurostimulation Appropriateness Committee (NACC) and the Neuromodulation Appropriateness Consensus Committee (NACC) (Deer et al. 2022; Deer et al. 2019; Deer et al. 2014). Although the 2008 NICE guideline (TA159) was published in 2008, it has been included because it was considered for review in 2014 and added to the ‘static guidance list’. The Scottish Intercollegiate Guidelines Network (SIGN) (2018) guideline does not make any recommendations for the use of SCS as a treatment option due to the uncertainty of the evidence available.

Only one relevant publication from Australia was identified in the search (Bates et al. 2019). The publication included a clinical algorithm for the management of chronic pain adapted from recommendations from various sources; however, it did not provide specific recommendations on the use of SCS. A number of guidelines for the purpose of accident compensation were also retrieved and these were not included. A summary of the included publications can be found in Appendix E.1, Table App 24.

## 5.2 Patient population

### 5.2.1 Clinical indications

There is little consensus in the recommendations on the patient population that should receive SCS. This may be attributed to the variability in pathologies that can result in patients developing chronic pain. Seven publications provided consensus and evidence-based recommendations on indications where SCS is recommended as a treatment option, including one publication on DRGS (Deer et al. 2019). In some cases where this is limited evidence, the use of SCS or DRGS needs to be assessed on a case-by-case basis (e.g., DRGS in patients with DPN [Deer et al. 2019] or SCS for patients with visceral pain [Deer 2014]). Table 23 summarises the patient populations recommended as ‘appropriate’ for treatment by SCS (excluding indications recommended on a case-by-case basis).

**Table 23** Recommended indications for SCS

	ASPN (USA) <i>Sayed 2022</i>	Dutch Consensus (Denmark) <i>Edelbroek 2022</i>	NACC (USA) <i>Deer 2019</i>	EAN (Europe) <i>Crucchi 2016<sup>b</sup></i>	NACC (USA) <i>Deer 2014</i>	ASIPP IPM Guidelines <i>Manchikanti 2013</i>	NICE 2008 (UK)
Chronic lower extremity pain						✓ <sup>d</sup>	
Chronic back and leg pain				✓			

	ASPEN (USA) <i>Sayed 2022</i>	Dutch Consensus (Denmark) <i>Edelbroek 2022</i>	NACC (USA) <i>Deer 2019</i>	EAN (Europe) <i>Cruccu 2016<sup>b</sup></i>	NACC (USA) <i>Deer 2014</i>	ASIPP IPM Guidelines <i>Manchikanti 2013</i>	NICE 2008 (UK)
Chronic low back pain	✓ <sup>e</sup>			✓		✓ <sup>d</sup>	
Complex regional pain syndrome <sup>a</sup>		✓	✓	✓	✓		✓
Failed back surgery syndrome		✓ <sup>c</sup>			✓		✓
Painful diabetic neuropathy/ polyneuropathy		✓		✓			
Refractory chronic cluster headache		✓					
Neuropathic groin pain			✓				
Other small fibre neuropathies		✓					

Abbreviations: ASPN, American Society of Pain and Neuroscience; ASIPP, American Society of Interventional Pain Physicians; EAN, European Academy of Neurology; IPM, Interventional Pain Management; NACC, Neuromodulation Appropriateness Consensus Committee/ the Neurostimulation Appropriateness Consensus Committee; NICE, National Institute of Health and Care Excellence; SCS, spinal cord stimulation.

**a** type I or II

**b** SCS added to CMM

**c** referred to as persistent spinal pain syndrome (PSPS) type 2 with arm or leg pain

**d** secondary to FBSS

**e** non-surgical low back pain

Note: indications that are recommended on a case-by-case basis have not been included

## Additional indications

Additional recommendations on patient populations where the use of SCS is appropriate has been included in three publications. The NACC recommends the use of cervical SCS for neuropathic pain syndromes affecting the upper extremities, such as radiculopathy (Deer et al. 2014), and for cervical radicular pain and upper extremity CRPS after failure of pharmaceutical or injection therapies (Deer et al. 2022). Cervical DRGS is recommended when pharmaceutical, injection and cervical SCS therapies have failed in patients with upper extremity neuropathic pain and CRPS (Deer et al. 2022).

The American Society of Pain and Neuroscience (ASPN) (Sayed et al. 2022) has also recommended that SCS is an appropriate treatment option following lumbar spinal surgery and in the treatment of patients with predominate lumbar spinal stenosis.

Lastly, Ziegler et al. (2022) characterised SCS as an invasive treatment option that should be reserved for patients with diabetic sensorimotor polyneuropathy who do not respond to analgesic combination pharmacotherapy.

### Refractory angina pectoris

Section 2.2.2 of this review discusses the inclusion of refractory angina pectoris as an indication for SCS based on the key MBS item for implantation (Item 39134). The included publications do not provide any recommendations that specifically endorse the use of SCS for the treatment of refractory angina pectoris. The NICE guideline (2008)'s evaluation of CLI and refractory angina pectoris does not recommend SCS as a treatment option for "chronic pain of ischaemic origin except in the context of research as part of a clinical trial".

## Device indications

The clinical indications and patient populations specified by device manufacturers for each of the SCS systems align with the recommendations from the included guidance documents. There is consensus amongst manufacturers that the SCS systems should be used in patients with “chronic intractable pain of the trunk and/or limbs”, with some manufacturers indicating specific neuropathic pain disorders. None of the devices have any indications for chronic pain of ischaemic origin, which is consistent with the recommendations from NICE (2008). The clinical indications and patient populations for each of the SCS systems are tabulated in Appendix E.2, Table App 25.

### 5.2.2 Eligibility criteria

Several of the recommended indications include additional criteria for SCS to be recommended as an appropriate treatment option. The NICE (2008) guideline recommends criteria that characterises the stage of chronic pain in adults (over 6 months) where CMM has not worked. The remaining additional criteria recommend that SCS be used as an alternative or when other treatment options have failed. The Dutch Consensus (Edelbroek et al. 2022) recommends for all five indications that neurostimulation, including SCS and DRGS, should be applied after conservative and minimally invasive treatment options have been exhausted. There appears to be consensus on this recommendation across five of the publications. Table 24 summarises the additional criteria required for use of SCS for the recommended indications.

**Table 24 Additional criteria for recommended indications appropriate for SCS**

Guideline developer (country)	Recommended indication	Additional criteria
Dutch Consensus (Denmark) <i>Edelbroek 2022</i>	PSPS (FBSS), CRPS, PDPN, other SFNs, medically refractory chronic cluster headache	Conservative treatments should be applied before neurostimulation. In the cause of insufficient effect on conservative treatments, minimally invasive treatment can be considered
NACC (USA) <i>Deer 2019</i>	FBSS	Absence of neurological progression requiring surgical intervention with persistent axial and radicular complaints
EAN (Europe) <i>Cruccu 2016</i>	CBLP	Alternative to reoperation in post-surgical CBLP
ASIPP IPM (USA) <i>Manchikanti 2013</i>	CLBP with lower extremity pain secondary to FBSS	After exhausting multiple conservative and interventional modalities
NICE 2008 (UK)	Chronic pain of neuropathic origin	Continue to experience chronic pain (measuring at least 50mm on a 0–100mm VAS) for at least 6 months despite appropriate conventional medical management
	FBSS	Alternative to repeat operation or increased opioid use
	CRPS	After pharmacotherapy and nerve blocks have been tried but have not provided adequate pain relief

Abbreviations: ASIPP, American Society of Interventional Pain Physicians; CBLP, chronic back and leg pain; CLBP, chronic low back pain; CRPS, complex regional pain syndrome; EAN, European Academy of Neurology; FBSS, failed back surgery syndrome; IPM, Interventional Pain Management; NACC, Neuromodulation Appropriateness Consensus Committee/ the Neurostimulation Appropriateness Consensus Committee; NICE, National Institute of Health and Care Excellence; PDN, painful diabetic neuropathy; PDPN, painful diabetic polyneuropathy; PSPS, persistent spinal pain syndrome; SFN, small fibre neuropathies, VAS, visual analogue scale

### 5.2.3 Patients unsuitable for spinal cord stimulation

Three publications have provided recommendations on patient populations that may be contraindicated or are unsuitable to receive SCS. Table 25 lists the recommendations for patients that are not recommended for SCS as a treatment option.

**Table 25 Recommendations on patients that are unsuitable or contraindicated for SCS**

Guideline developer (country)	Recommendation
NACC (USA) Deer 2019	Patients with significant psychological issues should be excluded or treated prior to consideration of DRGS. A history of sexual abuse or significant psychologic comorbidity should be considered a relative contraindication until proper counselling can be established and the therapist feels that an implant is indicated.
NACC (USA) Deer 2014	Patients with inadequately controlled psychiatric/psychological problems should not be implanted.
	Patients who cannot be taken off anticoagulants or bridged safely for the proper duration surrounding the trial or surgery should not undergo SCS or PNS.
	Patients in whom a systemic infection cannot be cured should not undergo implant.
	Patients in whom the treating physician does not have a strong working differential diagnosis in regard to the pain generator should not be implanted.
	In patients with platelet counts less than 50,000, SCS trials and implants should be avoided, unless managed in close collaboration with the treating haematologist.
	Patients with the inability to cognitively participate in their care should not be implanted. In partially impaired patients, implant may be acceptable if the primary caregiver is able to participate actively. Non-rechargeable batteries should be considered in this second group of patients.

Abbreviations: DRGS, dorsal root ganglion stimulation; NACC, Neuromodulation Appropriateness Consensus Committee/ the Neurostimulation Appropriateness Consensus Committee; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation.

## 5.3 Management pathways

Four publications have provided recommendations on the place of SCS in the chronic pain clinical management pathway. The NACC recommended that SCS should be considered early in the course of the disease process and that clinical assessment prior to SCS implantation should include “a psychological assessment to address any concerning psychiatric comorbidities” (Deer et al. 2014) and “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” (NICE 2008). Contrary to the recommendations from the NACC (Deer et al. 2014), Bates (2019) produced a clinical algorithm pathway that placed SCS as a fourth line treatment for neuropathic pain following inadequate response to first (tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, gabapentanoids, and topicals), second (tramadol and combination first line therapies), and third line therapies (serotonin-specific reuptake inhibitors/anticonvulsants/NMDA antagonists and interventional therapies such as epidural injection) and 50% pain relief after a trial stimulation.

### 5.3.1 Types of spinal cord stimulation

Two publications provided recommendations on criteria for selecting conventional, high-frequency or burst SCS devices. The NACC (Deer et al. 2014) recommends that conventional SCS or DRGS should be selected in patients with pain that is predominantly radicular, while high-frequency SCS or burst SCS may be appropriate for patients with axial back pain and tonic stimulation resistance. It is also recommended that DRGS is “superior to standard tonic SCS for unilateral focal pain caused by CRPS I and II in the lower extremity” (Deer et al. 2019).

NICE has released ‘medical technologies guidance’ (MTG) on the Senza SCS system (Nevro) that provides recommendations for delivering high-frequency (HF10) therapy to patients with chronic neuropathic back or leg pain after FBSS. The MTG advises that the Senza HF10 system “is at least as effective as low-frequency SCS in reducing pain and functional disability” (based on evidence from 10 studies, including 2 RCTs) and does not cause paraesthesia. In order for patients to be eligible for the device, patients must have failure of CMM prior to implantation (NICE 2019).

NICE have also released a number of ‘medtech innovation briefings’ (MIB) that have evaluated individual SCS systems. The guidance from these briefings is tabulated in Table 26.

**Table 26 NICE medtech innovation briefings for SCS systems**

MIB	Title	NICE conclusions
NICE 2022 MIB305	Differential target multiplexed spinal cord stimulation for chronic lower back and leg pain	The intended place in therapy would be as an alternative to traditional SCS in adults with chronic, intractable, lower back and leg pain. Experts advised that DTM SCS is a minor innovative variation of traditional SCS, which could however, provide pain relief and improvements in quality of life to people. They also noted that few patients with chronic intractable pain currently receive SCS.
NICE 2020 MIB238	Evoke Spinal Cord Stimulator for managing chronic neuropathic or ischaemic pain	The intended place in therapy would be as a replacement or alternative to current open-loop (fixed-output) SCS therapy in people with leg and back pain. Evoke is more effective than open-loop SCS in people with intractable back and leg pain.

Abbreviations: DTM, differential target multiplexed; NICE, National Institute for Health and Care Excellence; SCS, spinal cord stimulation

### 5.3.2 Trial stimulation

There is consensus between the four publications that a trial stimulation is recommended prior to permanent implantation of an SCS device. The NACC also recommends a “trialing methodology” for DRGS in “painful areas with coverage of bilateral complaints bilaterally” (Deer et al. 2019), and for cervical SCS in patients with cervical radicular pain with or without cervical axial neck pain and without clear surgical pathology (Deer et al. 2022). A trial stimulation is recommended to take place within the first two years of chronic pain and a successful trial is defined as “the patient having had at least 50% pain relief” (Deer et al. 2014). This is supported by NICE (2008), which recommends that implantation “should follow only after a successful trial of stimulation”.

Regulatory advice published by the U.S Food and Drug Administration (FDA) (2020) recommends that:

- Permanent SCS should only be implanted in patients who have undergone and passed a stimulation trial.
- Health care providers typically perform a stimulation trial on a patient for 3-7 days.
- Similar to NACC advice (Deer et al. 2014), success is usually defined by a 50% reduction in pain symptoms.

# 6 Summary of findings and considerations for MDHTAC

## 6.1 Comparative clinical effectiveness

The findings relating to the comparative clinical effectiveness of SCS are based on three SRs, supplemented by studies provided by sponsors and stakeholders. The SRs are:

- Traeger (2023) Cochrane review: assessment of SCS in people with low back pain
- O’Connell (2021) Cochrane review: assessment of SCS in people with chronic pain
- NICE (2008): assessment of SCS in ischaemic pain.

The evidence from the Traeger (2023) and O’Connell (2021) reviews are overlapping and were supplemented with additional studies from sponsors and stakeholders, and the findings of all are considered together in this section.

The NICE review was included to address an evidence gap (given the inclusion of patients with refractory angina in the MBS item descriptors) and is considered separately.

### 6.1.1 Spinal cord stimulation in people with chronic (non-ischaemic, non-cancer) pain

#### Cochrane systematic reviews

Two Cochrane SRs considering the effectiveness of SCS were recently published and provide the most recent and comprehensive summary of the available evidence. The two reviews have substantial overlap in methodology and include eight of the same studies.

#### Summary of Traeger 2023

The findings by outcome and follow-up time (medium and long term only) for SCS compared to either placebo (sham stimulation) or as an addition to medical management for the treatment of low back pain are summarised in Table 27. The summary includes the number of RCTs and participants, and the author’s assessment of the quality of the evidence.

**Table 27 Summary of findings in Traeger (2023) at medium- (M) and long- (L) term follow-up**

Outcomes	No. RCTs; N	Quality of evidence	Statistical significance	Clinical importance <sup>a</sup>
<b>SCS versus placebo(sham)</b>				
<b>Pain intensity</b>				
Low back pain	1; N=50 (M)	moderate	No effect	No difference
Leg pain	1; N=50 (M)	moderate	No effect	No difference
<b>Function</b>	1; N=50 (M)	moderate	No effect	No difference
<b>HRQoL</b>	1; N=50 (M)	moderate	No effect	No difference
<b>SCS + MM versus MM alone</b>				
<b>Pain intensity</b>				
Low back pain	3; N=430 (M)	very low	No effect	Favours SCS
Leg pain	2; N=290 (M)	very low	Favours SCS	Favours SCS
≥50% better	3; N=430 (M)	very low	Favours SCS	Favours SCS
	1; N=100 (L)	very low	Favours SCS	Favours SCS



Outcomes	No. RCTs; N	Quality of evidence	Statistical significance	Clinical importance <sup>a</sup>
<b>Function</b>	3; N=430 (M)	low	Favours SCS	Favours SCS
<b>HRQoL</b>	2; N=289 (M)	very low	No effect	NR
<b>Harms</b>				
AEs	2; N=336 (M)	very low	Favours SCS	NR
SAEs	1; N=140 (M)	low	No effect	NR
<b>Secondary outcomes</b>				
Opioid use	2; N=290 (M)	low	Favours SCS	NR
Daily MMEs	3; N=430 (M)	low	No effect	NR

Source: based on data from Traeger (2023) Cochrane review

Abbreviations: AE, adverse event; HRQoL, health-related quality of life; MM, medical management; MMEs, morphine milligram equivalents; N, population; NR, not reported; RCT, randomised controlled trial; SAE, serious adverse event; SCS, spinal cord stimulation

<sup>a</sup> Clinical importance is defined by a predetermined threshold of  $\geq 10$  points for pain intensity (derived from O'Connell 2021) and function (derived from Hara 2022).

Key: orange = very low quality evidence; yellow = low quality evidence; blue = moderate quality evidence; green = favours intervention.

(M) = medium-term outcomes  $\geq 3$  months to  $< 12$  months; (L) = long-term outcomes  $\geq 12$  months.

### Summary of O'Connell, 2021

The findings by outcome and follow-up time (medium and long term only) for SCS in addition to medical management for the treatment of chronic pain are summarised in Table 28. The summary includes the number of RCTs and participants, and the author's assessment of the quality of the evidence. No outcomes with medium-term or greater follow-up were identified for studies of SCS compared to placebo.

**Table 28 Summary of findings in O'Connell (2021) at medium- (M) and long- (L) term follow-up**

Outcomes	No. RCTs; N	Quality of evidence	Statistical significance	Clinical importance <sup>a</sup>
<b>SCS versus placebo (sham)</b>				
<i>no evidence at medium or long-term follow-up</i>				
<b>SCS + other intervention (MM or physical therapy) versus other intervention alone</b>				
<b>Pain intensity</b>				
Continuous outcomes (VAS 0-100)	5; N=634 (M)	low	Favours SCS	Favours SCS
<i>mean difference</i>	1; N=44 (L)	very low	No effect	No difference
Proportion with $\geq 50\%$ pain relief	5; N=597 (M)	low	Favours SCS	Favours SCS
	1; N=87 (L)	very low	Favours SCS	Favours SCS
<b>AEs</b>				
Lead failure/displacement	3; N=330 (M)	very low	No effect	NR
	1, N=44 (L)	very low	Favours MM	NR
Infection	4; N=548 (M)	low	Favours MM	NR
Reoperation/reimplantation	4; N=548 (M)	very low	Favours MM	NR
	1; N=44 (L)	very low	Favours MM	NR
Other AEs	2; N=278 (M)	low	No effect	NR
	1; N=100 (L)	very low	No effect	NR
<b>Secondary outcomes</b>				
Disability	2; N=312 (M)	very low	No effect	No difference
HRQoL	5; N=595 (M)	low	Effect in favour of SCS	NR
	1; N=44 (L)	very low	No effect	No difference
Medication use	2; N=154 (M)	low <sup>b</sup>	No effect	No difference

Source: based on data from O'Connell (2021) Cochrane review

Abbreviations: AE, adverse event; HRQoL, health-related quality of life; MM, medical management; N, population; NR, not reported; RCT, randomised controlled trial; SCS, spinal cord stimulation; VAS, visual analogue scale.

**a** Clinical importance is defined by a predetermined threshold of  $\geq 10$  points for pain intensity (derived from O'Connell 2021) and function (derived from Hara 2022).

**b** very low certainty of evidence on anticonvulsants, low for other medication types.

Key: orange = very low quality evidence; yellow = low quality evidence; blue = moderate quality evidence; green = favours intervention; pink = favours comparator.

(M) = medium-term outcomes  $\geq 3$  months to  $< 12$  months; (L) = long-term outcomes  $\geq 12$  months.

## Discussion

The two Cochrane reviews conclude that SCS may not be beneficial in their respective populations. This is based on differences in findings aligning with methodological differences in the study designs across the included RCTs and is discussed extensively in O'Connell (2021).

Studies of SCS compared to sham treatment were relatively small, of short-term duration and at high risk of bias. O'Connell particularly emphasises the lack of formal assessment of blinding success, the common use of per-protocol analyses and the lack of washout periods, and further notes that the included populations are often participants who had already demonstrated a positive response to SCS. Despite these potential sources of bias, sham-controlled studies reported only small, possibly clinically insignificant effects; where analyses were restricted to studies that were adequately blinded, there was no evidence for a treatment effect.

In contrast, open-label comparisons to conventional management demonstrated large, clinically significant effects. O'Connell states that this *“raises questions regarding the mechanisms of SCS and how much of the observed effect might be explained by the contextual effects of undergoing this complex and invasive clinical procedure, rather than the specific effects of SCS. It might be argued that contextual (placebo) effects are unlikely to account for such large and sustained effects. However, the use of sophisticated technology, the invasive nature of the procedure, the need for frequent clinical interactions and treatment-related sensory experiences and, in some cases, the costs of [SCS] all have the potential to drive non-specific effects.”*

A key difference between the two Cochrane reviews is the inclusion of the Hara (2022) study, which was published after the O'Connell (2021) review but is included in Traeger (2023) and is pivotal to their conclusions. Hara (2022) is a cross-over RCT comparing burst SCS with placebo (sham) SCS in 50 patients with chronic radicular pain. Participants underwent two three-month periods with each condition and therefore it is the only study that provides medium-term outcomes for the placebo comparator. The study reported no significant differences between SCS and placebo for any outcomes (Table 27). Traeger (2023) rated the quality of this evidence as moderate and rated this study at low risk of bias overall. The quality of the evidence was downgraded one level (from high) due to 'possible differences between the burst SCS regimen provided in the trial and other SCS regimens provided internationally.'

The Hara RCT (2022) has been strongly critiqued in the literature (De Ridder 2023; North and Shipley 2023; JAMA letters) and elsewhere<sup>15</sup>. Although the critiques present a number of concerns, a consistent issue is the validity of the SCS as applied in the active stimulation arm of the trial. The authors label this stimulation 'burst' (described as closely spaced, high frequency stimuli delivered to the spinal cord; the stimulus consisted of a 40 Hz burst mode of constant current with 4 spikes per burst at an amplitude corresponding to 50% to 70% of paraesthesia perception threshold); however, it differs from BurstDR™ stimulation (De Ridder, 2023<sup>16</sup>), raising concerns that the trial was a 'placebo versus placebo' trial. Eldabe (2023) cites their own study (Eldabe 2020) in support of this conclusion.

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<sup>15</sup>For example on the Neuromodulation Society of Australia and NZ at: <https://www.nsan.org.au/wp-content/uploads/2022/12/Response-to-Recent-JAMA-Article-on-Spinal-Cord-Stimulation.pdf>

<sup>16</sup>Note that De Ridder has the IP on BurstDR™

Eldabe (2020) is a small (n=19), short-term (two weeks per treatment), cross-over RCT of conventional SCS, 'burst' SCS and placebo, which found no effect for 'burst' compared to placebo (MD in pain intensity 2.55 [95% CI -7.64 to 12.74]) but did find an effect for conventional SCS compared to placebo (MD -12.75 [95% CI -20.39 to -5.11]) (results as reported by Traeger [2023]).

Other criticisms of Hara (2022) are less fundamental. For example, criticism of the trial implant methodology may be legitimately queried (the outcome for success was low at  $\leq 30\%$  pain reduction and conventional SCS was used) but the use of a trial stimulation itself has been queried in the literature given the uniformly high rate of success (see for example, TRIAL-STIM [Eldabe, 2020]) and the authors report in their response to criticism that the mean improvement was 63% (Gulati 2023).

Similarly, the lack of a washout period is replicated in the majority of sham-controlled trials and the longer duration of treatment in Hara (2022) would be expected to reduce the risk of bias from this compared to shorter treatment duration trials.

Despite the critiques, the Hara trial (2022) does have a strong methodological design and the success of blinding was reported (correct treatment allocation guess in 58%). The limitations are in the applicability of the stimulation parameters and, as noted by the authors, the prohibition on any change to the parameters during treatment to preserve blinding (which differs to clinical practice).

There have also been negative critiques of the Cochrane reviews. The O'Connell review (2021) includes multiple patient populations and although Traeger (2023) is less broad, there are differences in patient populations across the included studies, for example patients with failed surgery in some trials and patients who had not had surgery in another. Furthermore, both reviews include different types of SCS devices and although subgroup analyses were planned, the authors were restricted by the volume of evidence available. Subgroup analyses of high-frequency, burst and conventional SCS were explored in both reviews but no evidence in favour of one stimulation type was found.

Given the concerns that the Cochrane reviews had narrow inclusion criteria that omitted a much larger volume of relevant evidence, additional RCT and appropriately adjusted comparative observational studies were considered as supplementary evidence in this PLR.

## Supplementary evidence

### Randomised controlled trials

All evidence provided by sponsors and stakeholders, together with evidence excluded from the Cochrane reviews, was collated for this PLR. Nine additional RCTs were considered as they provided at least medium-term follow-up (three months or more) and reported a measure of pain intensity. These studies are provided as supplemental evidence, not as part of a formal SR. The findings from the additional RCTs, for pain outcomes only, are summarised in Table 29.

Although small differences in pain outcomes were found for some trials, all favouring the intervention, many reported no difference. Two of the nine trials stated they were blinded, one of which reported no difference between multicolumn SCS programming and conventional SCS in patients with FBSS (ESTIMET). The second blinded RCT (EVOKE), which was in patients with chronic intractable pain of the back and legs, reported a difference in favour of closed-loop SCS in responder analysis and mean change in pain intensity. Although these trials demonstrate a significant reduction in pain intensity between baseline and follow-up across both arms, the blinding within them is to the intervention and not to the use of SCS; therefore, this does not add confidence regarding overall clinical effectiveness of SCS compared to standard (non-SCS) treatment.

DRGS stimulation is in scope of this PLR and was in scope for O'Connell (2021), although no studies of this stimulation type met their inclusion criteria. Therefore, the ACCURATE RCT (Deer 2017) is the best available evidence on these devices. The ACCURATE study demonstrated that DRGS may be more favourable than

SCS for pain outcomes in patients with CRPS; however, DRGS also had higher rates of AEs. Although non-significant, the authors attributed this to a longer procedure time and a greater number of implanted leads (3 or 4 compared to 1 or 2).

**Table 29 Summary of findings of additional RCT evidence at medium- (M) and long- (L) term follow-up**

Outcome	Study ID	Blinding	Statistical significance	Clinical importance <sup>a</sup>
<b>HF-SCS versus conventional SCS</b>				
Pain intensity (mean change)	SURF (Bolash 2019)	None	No effect (M)	No difference
	Canós-Verdecho (2021)	None	NR (M, L)	No difference
	De Andres (2017)	Partial	No effect (M, L)	No difference
	SENZA-RCT (Kapural 2015; Kapural 2016)	None	Favours HF-SCS (L)	Favours HF-SCS (back pain)
Pain intensity (≥ 50% relief)	SURF (Bolash 2019)	None	No effect (M)	No difference
	SENZA-RCT (Kapural 2015; Kapural 2016)	None	Favours HF-SCS (L)	Favours HF-SCS (back pain)
<b>DRGS versus conventional SCS</b>				
Pain intensity (mean change)	ACCURATE (Deer 2017)	None	NR (M, L)	Borderline Favours DRGS
Pain intensity (≥ 50% relief)	ACCURATE (Deer 2017)	None	Favours DRGS	Favours DRGS
<b>MCP SCS versus conventional SCS</b>				
Pain intensity (mean change)	ESTIMET (Rigoard 2021)	Yes	No effect (M)	No difference
Pain intensity (≥ 50% relief)	ESTIMET (Rigoard 2021)	Yes	No effect (M)	No difference
<b>Closed-loop SCS versus conventional SCS</b>				
Pain intensity (≥ 50% relief)	EVOKE (Mekhail 2020; Mekhail 2022)	Yes	Favours closed-loop (M, L)	Favours closed-loop
<b>DTM SCS versus conventional SCS</b>				
Pain intensity (mean change)	Fishman (2021)	None	No effect (M)	No difference
Pain intensity (≥ 50% relief) - back	Fishman (2021)	None	Favours DTM (M, L)	Favours DTM
Pain intensity (≥ 50% relief) - leg	Fishman (2021)	None	No effect (M, L)	No difference
<b>Burst SCS versus conventional SCS</b>				
Pain intensity (mean change)	SUNBURST (Deer 2018; D'Souza 2021)	None	Favours Burst (M)	No difference

Abbreviations: DRGS, dorsal root ganglion stimulation; DTM, differential target multiplexed; HF, high-frequency; L, long-term outcomes; M, medium-term outcomes; MCP, multicolumn programming; SCS, spinal cord stimulation

<sup>a</sup> Clinical importance is defined by a predetermined threshold of ≥10 points for pain intensity (derived from O'Connell 2021).

Key: orange = partially blinded; yellow = open-label; blue = blinded; green = favours intervention

### Non-randomised comparative studies

Five additional non-randomised comparative cohort studies were identified from stakeholder and sponsor submissions, of which only two were large, appropriately adjusted registry studies that provided useful information. The two large registry studies (Dhruva 2023; Vu 2022) both reported minimal differences in opioid consumption between large propensity matched cohorts (SCS compared to no SCS), none of which were considered clinically significant. Rates of implant removal or revision were 22.1% in Dhruva (2023).

The findings of Dhruva (2023) have been strongly refuted in the literature (Deer 2023) and by some stakeholders, while being supported by other stakeholders. The criticisms range from flaws in study design, inadequate propensity matching criteria and flawed interpretation of findings. The nature of the authorship

has also been questioned, being mainly employees of Optum Health, the owner of the Optum Health Insurance Industry database, and lacking any pain specialists<sup>17</sup>.

A major criticism is that patients in the SCS group are, by definition, further along in the treatment algorithm than the CMM patients, since they have failed CMM prior to qualifying for SCS. Therefore, the comparison is being made between SCS patients refractory to CMM with those undergoing CMM, which is claimed to be an inappropriate comparison. It has been pointed out that reductions in pain surrogates would be expected in both groups from the first year to the second year of follow-up as they move through their treatment pathways, consistent with an expected positive response to various treatments over time for many patients, and this was observed (Deer 2023). The rate of this reduction cannot be expected to be the same for both groups, so comparing them is not a meaningful analysis. Further confounding this comparison is the allowance for patients to receive their SCS implant up to one year from the index date, meaning their first year of opioid use may coincide with the year prior to implant rather than the first-year post-implant (Deer 2023).

As the design of Vu (2022) is similar to that of Dhruva 2023, it is presumed to have the same limitations as described above (e.g., the cohorts being compared will include patients at different points in the clinical management pathway, and an arbitrary threshold for a surrogate pain outcome does not necessarily capture the clinical picture).

For many clinical questions, propensity matched cohorts derived from large registry databases can provide powerful insights. However, the lengthy, multi-stepped nature of the clinical management pathway for chronic pain may not lend itself well to registry database analyses, which tend to lack granularity and specificity. However, if propensity matched cohorts are considered inadequate, then appropriate RCTs of high methodology quality will be even more vital to understanding the comparative effectiveness of SCS devices.

### 6.1.2 Spinal cord stimulation in people with ischaemic pain

The NICE (2008) SR of SCS in people with ischaemic pain included eight RCTS (four for CLI and four for angina). The findings were equivocal, and NICE did not recommend SCS for these indications. No stakeholders or sponsors provided additional information to support SCS in these indications.

## 6.2 Comparative cost-effectiveness

The available evidence on the comparative cost-effectiveness of SCS was provided by a SR by Niyomsri (2020), with only a single additional study identified in the peer-reviewed literature (Rojo 2021). Across these studies, the findings demonstrate that although initial costs of SCS devices are high, studies with longer time horizons tend to report that SCS is cost effective as the modelled improvement in health outcomes is extrapolated over this timeframe. Niyomsri (2020) notes that the models were limited by a lack of long-term clinical data and missing follow-up costs.

An Australian cost-effectiveness study (commissioned by NSANZ) was also identified (Deloitte 2019). A Markov model was used to compare treatments in FBSS and CRPS patients. From a health system perspective, SCS devices were considered cost effective in the treatment of FBSS and CRPS (type I) when compared to usual care. The ICER was \$15,070 per QALY gained for patients with FBSS and \$2,321 per QALY gained for patients with CRPS. The model was most sensitive to the time horizon, discount rate, ongoing costs of treatment in the SCS arm, and device longevity.

The clinical evidence underpinning the Australian economic analysis is the PROCESS trial (Kumar 2007), which is an open-label RCT of SCS versus CMM in 100 patients with FBSS. The trial was included in both

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<sup>17</sup> Noting that the author of Deer (2023) also has conflicts of interest reporting personal fees from Abbott, Boston Scientific and Saluda amongst others and has a patent for DRG leads pending to Abbott.

Cochrane reviews (O’Connell 2021; Traeger 2023). As these reviews noted, sham-controlled trials generally reported a smaller effect in favour of SCS than open-label trials. Furthermore, although the PROCESS study had follow-up to 2 years, extrapolation to 15 years introduces significant uncertainty with respect to both the durability of treatment effects and ongoing AE rates.

The PL benefits for SCS devices and their accessories on the PL have remained unchanged following benchmarking by the Independent Hospital Pricing Authority (IHPA) as a component of the PL reforms<sup>18</sup>. This may not be informative regarding whether PL benefits differ from those in the public system given that SCS is largely restricted to the private system. The included economic studies did not identify information regarding current unit costs in other countries. A Canadian HTA (Ontario Health 2020) estimated that SCS device costs in Ontario averaged \$24,464 (2018 Canadian dollars) including the IPG, leads and other surgical tools. In the Belgium list of reimbursable devices<sup>19</sup>, the benefit for an IPG for neurogenic pain ranges from €5,227 to €17,334.

Given the clinical uncertainty, cost-effectiveness analysis to establish a suitable benefit for SCS devices is unlikely to be informative. There is no evidence to recommend a change to the SCS benefits on the PL.

### 6.3 Patient selection and management

No recent, high quality Australian clinical practice guidelines were identified in the search, although an Australian clinical algorithm was identified (Bates 2019). There was moderate consistency across the identified guidelines from other countries. For example, most recommended SCS for CRPS and FBSS, but there were variations on recommended indications beyond these. Similarly, there was a consistent thread that SCS should only be used following failure of conservative treatment options, but the guidance varied in the definition of treatment failure and the point in the treatment pathway where SCS is considered an appropriate option. Most guidelines were consensus-based and the extent to which they would be applicable to Australian clinical practice is uncertain.

### 6.4 Considerations for MDHTAC

Although triggered by AE reports (Jones et al. 2022), this PLR has focused on the comparative clinical effectiveness and cost-effectiveness of SCS with the understanding that the TGA is concurrently undertaking a post-market review and will consider safety.

The evidence base for the comparative clinical effectiveness of SCS compared to standard care is uncertain. Despite the large number of RCTs conducted of the devices, there remains doubt as to the magnitude of their clinical effect and the long-term risk of AEs.

The uncertainty in the evidence base is disappointing given the volume of evidence and it is important that further studies do not replicate the type of studies that have already been undertaken. However, it is understood that study design is frequently driven by regulatory requirements in which comparison of a modified device to a predicate is sufficient for market access and, in some cases, also for reimbursement. Furthermore, the generation of evidence, and its interpretation, is highly contested and there are few authors or funders without significant commercial or other conflicts of interest.

Patients with chronic pain are heterogeneous and complex, with comorbidities and mental health problems often co-occurring. It is estimated that one in five Australians live with chronic pain,<sup>20</sup> with considerable impacts on people’s ability to work and participate in society. In this diverse population, it is notoriously challenging to generate high-level evidence of efficacy, particularly during later lines of treatment. This PLR

<sup>18</sup> See <https://www.health.gov.au/resources/publications/advice-on-the-prostheses-list-adjusted-benefit-amounts>

<sup>19</sup> Available at: <https://www.riziv.fgov.be/fr/professionnels/sante/fournisseurs-implants/Pages/implants-liste-prestations-nominatives.aspx>

<sup>20</sup> National Strategic Action Plan for Pain Management available at: <https://www.painaustralia.org.au/static/uploads/files/national-action-plan-final-02-07-2019-wfpnnlamkiqw.pdf>

is not a comprehensive SR, nor has it delved into mechanistic understandings of SCS therapies, patient selection models or similar questions, which all may provide valuable insights. However, the PLR has considered additional comparative evidence excluded from the Cochrane reviews, and no additional studies were identified that would alter those conclusions.

In light of the uncertainty in the evidence base for SCS, it is recommended that MDHTAC continue to list SCS devices on the PL, with no further increases in Benefit, whilst also undertaking further actions. The following actions are considered critical and are in line with the recommendations of the MBS Review Taskforce. To achieve these actions, MDHTAC may need to work with the TGA, MSAC, Australian Commission on Safety and Quality in Health Care (ACSQHC) and other stakeholders.

#### 1. Development of high-quality clinical guidelines

The need for clinical guidelines for SCS devices was clearly articulated in the MBS Review Taskforce recommendations (2019) where it was noted that good outcomes were likely restricted to a very select patient population, and that patient selection and follow-up are critical but are difficult to include in an item descriptor. The development of clinical practice guidelines could bring together stakeholders, patients and clinical experts to fill a critical gap, bridging the uncertainty in the evidence with the need to make the best possible decisions in clinical practice. Furthermore, clinical practice guidelines can take a broader perspective on chronic pain treatment and management, with consideration of multidisciplinary approaches to patient care that address biological, psychological and social factors.

The MBS Review Taskforce stated that clinical guidelines for implantable devices for pain management are currently under development by the Australian and New Zealand College of Anaesthetists (ANZCA) Faculty of Pain Medicine. It is further noted that the ACSQHC has clinical care standards on both analgesic stewardship in acute pain<sup>21</sup> and low back pain<sup>22</sup> (up to 12 weeks); although neither are directly relevant, it suggests a gap and an opportunity for collaboration. The National Strategic Action Plan for Pain Management should also be considered as a starting point as it states that goal three is that ‘health practitioners are well-informed and skilled on best practice evidence-based care and are supported to deliver this care.’

The development of any clinical guidelines needs to incorporate communication with MDHTAC and MSAC to ensure that listings are kept consistent with recommended clinical practice. For example, no evidence was found to support the use of SCS in refractory angina and this could be removed from MBS item descriptors if usage for this indication is not recommended in clinical guidelines.

#### 2. Improved data monitoring and development of a national registry

The TGA clinical evidence guidelines on medical devices notes that device registries ‘play a unique and important role in medical device surveillance<sup>23</sup>’, noting the examples of the Australian Breast Device Registry (ABDR), the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) and the Victorian Cardiac Outcomes Registry (VCOR). Given the high cost, invasive nature and ongoing uncertainty regarding SCS, they are good candidates for inclusion within a registry.

There is an international registry of Boston SCS devices (Rauck 2023) that has reported adverse event rates, and also a registry of Abbott devices (NCT03876054). Although these are limited to, and funded by single manufacturers, they could provide valuable information if there is data transparency and high-quality data capture. Internationally, there is also a UK and Ireland National

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<sup>21</sup> Available at: <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/opioid-analgesic-stewardship-acute-pain-clinical-care-standard-2022>

<sup>22</sup> Available at: <https://www.safetyandquality.gov.au/publications-and-resources/resource-library/low-back-pain-clinical-care-standard-2022>

<sup>23</sup> Available at: <https://www.tga.gov.au/sites/default/files/clinical-evidence-guidelines-medical-devices.pdf>

Neuromodulation Registry<sup>24</sup> and a Danish registry, the Aarhus Neuromodulation Database (Meier, 2013).

In Australia, the electronic Persistent Pain Outcomes Collaboration (ePPOC)<sup>25</sup> collects, analyses, and reports standardised data from pain management services and is supported by the Faculty of Pain Medicine. An option is to consider capturing SCS outcome data within the existing electronic ePPOC initiative of the Faculty of Pain Medicine, thereby allowing comparison of outcomes from SCS with non-surgical treatments. It is understood that registries can be costly and challenging to establish and maintain, and that priorities need to be set. Work in both clinical and medical device registries has been undertaken<sup>26</sup>, and this recommendation needs to be considered within that context.

In the absence of a national registry or extension to the ePPOC data collection, there is valuable information already available for monitoring the use of SCS devices and monitoring should be undertaken proactively. In particular, MBS data could be used to understand current patient profiles and links between insertions and removals (rates and timeframes). Consideration could be given to having a separate MBS item for IPG replacement due to battery end of life to differentiate this from removal due to lack of efficacy or other reasons. A similar MBS item exists for vagal nerve stimulation (item 40708) 'surgical replacement of battery in electrical pulse generator'.

### 3. High-quality research

Conducting further trials of the same design will not resolve the outstanding uncertainty. Sponsors, researchers, and funders should all be encouraged to design studies that are methodologically rigorous, well conducted and reported, and answer priority questions. This may include the use of individual patient data or large registries, but it may also require a double blinded RCT of similar design to Hara (2022) using a different paraesthesia-free treatment arm.

There are a number of ongoing clinical trials of SCS (refer to Appendix C.1.1, Table App 5 and Table App 6) and it is recommended that MDHTAC continue to monitor the outcomes of these.

These recommendations are supported by Pain Australia, the national peak body working to improve the quality of life of people living with pain, their families and carers. Pain Australia has recently undertaken a survey on consumer experiences of SCS that will be reported in late 2023 and should be considered by MDHTAC alongside the PLR.

PNS devices were determined to be out of scope for this review. Two devices are currently listed on the PL in the same grouping as SCS. It is therefore recommended that PLAC:

- create a separate group for PNS devices for chronic pain;
- undertake focussed HTA of these devices to ensure they are appropriate for ongoing listing on the PL or refer them to MSAC for assessment;
- consider the appropriateness of leads with dual approval for SCS and PNS indications.

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<sup>24</sup> See <https://nsuki.memberclicks.net/assets/documents/Patient%20Information%20NNR%20160118.pdf>

<sup>25</sup> See <https://www.uow.edu.au/ahsri/eppoc/>

<sup>26</sup> See the ACSQHC for 'National Arrangements for clinical quality registries' at <https://www.safetyandquality.gov.au/our-work/health-and-human-research/national-arrangements-clinical-quality-registries> and the Clinical Registers for High Risk Implantable Medical Devices – Regulation Impact Statement at <https://oia.pmc.gov.au/published-impact-analyses-and-reports/clinical-registers-high-risk-implantable-medical-devices-0>



## 6.5 Considerations for MSAC

The MBS is legally enforceable and has greater scope than the PL for specifying conditions of use. The MBS Review Taskforce (2019) stated that:

“due to the evolving evidence regarding what population groups benefit from these procedures, these item numbers should be reviewed in 2 years to ensure ongoing evidence based applicability”

An MBS review is considered critical and is overdue. The review could consider the ongoing listing of SCS services on the MBS broadly and/or specific changes to the MBS items to improve monitoring and target appropriate claiming. Possible changes to MBS items are outlined below:

- The introduction of a separate MBS item for implantable pulse generator (IPG) replacement due to battery end of life (see recommendation 2).
- Clarification of the two MBS items for peripheral lead implantation
  - Surgical lead implantation has a higher benefit than percutaneous lead implantation. The item number for percutaneous lead implantation (39129) was introduced following the MBS Review Taskforce (2019), which identified no item for this purpose. However, utilisation is extremely low suggesting the surgical item continues to be claimed (see Figure 2). Sponsors have stated that surgical placement is not used for PNS.
- The introduction of, and mandated use of, item numbers for trial stimulation including the specification that trial leads be used.
- Removal of refractory angina as an indication for SCS, given the absence of evidence to support this indication. Alternately, creation of separate item numbers to monitor this indication.
- A restriction to once per lifetime for initial implantation of an SCS device.
- A requirement for a multidisciplinary team conference prior to initial implantation of an SCS device to discuss patient suitability for the intervention.

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# Appendix A PL grouping of 'Neurostimulation Therapies for Pain' Subcategory

**Table App 1 Grouping of SCS, DRGS, and PNS systems in the PL (November 2022)**

Group	Subgroup	Device Name	Sponsor	Billing Code	Benefit	ARTG
<b>Neurostimulators</b>						
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	Precision Novi IPG	Boston Scientific Australia Pty Ltd	BS322	\$21,660	283692 283693
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	WaveWriter Alpha	Boston Scientific Australia Pty Ltd	BS383	\$21,660	362970 362971
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	Proclaim IPG	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ379	\$21,660	279015 279016
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	Proclaim DRG	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ389	\$21,660	289235 333461
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	Proclaim XR IPG	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ432	\$21,660	351631 351632
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	PrimeAdvanced Surescan MRI Neurostimulator	Medtronic Australasia Pty Ltd	MI135	\$17,283	215751
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	Axiom Neurostimulator System - Implantable Neurostimulator	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ362	\$17,283	202323
04.05.01 - Pulse Generators	04.05.01.01 - Primary Cell Pulse Generator (non-rechargeable)	Reactiv8 Implantable Pulse Generator	MAINSTAY MEDICAL (AUSTRALIA) PTY LIMITED	PQ004	\$17,283	327089 <sup>b</sup>
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	RestoreSensor Surescan MRI Neurostimulator	Medtronic Australasia Pty Ltd	MI132	\$21,660	215750
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Intellis AdaptiveStim Neurostimulator	Medtronic Australasia Pty Ltd	MI274	\$23,465	298746
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Evoke Closed Loop Stimulator (CLS)	SALUDA MEDICAL PTY LIMITED	UY003	\$23,465	336330
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Precision Spectra IPG	Boston Scientific Australia Pty Ltd	BS254	\$23,465	205793
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Precision Spectra WaveWriter IPG	Boston Scientific Australia Pty Ltd	BS362	\$23,465	318260
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	WaveWriter Alpha	Boston Scientific Australia Pty Ltd	BS389	\$23,465	362972 362973
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Precision Montage MRI IPG	Boston Scientific Australia Pty Ltd	BS330	\$23,465	286709
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Prodigy IPG	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ374	\$23,465	230721 279911
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Intellis Neurostimulator	Medtronic Australasia Pty Ltd	MI275	\$23,465	298747
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Senza II IPG Kit	Emergo Asia Pacific Pty Ltd	ER496	\$23,465	186043
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	Senza Omnia IPG Kit	Emergo Asia Pacific Pty Ltd	ER535	\$23,465	330704
04.05.01 - Pulse Generators	04.05.01.02 - Rechargeable Pulse Generator	StimRouter Neuromodulation System Kit	ALGOSTIM RESEARCH AND DEVELOPMENT PTY LIMITED	FP001	\$18,032	313344 <sup>b</sup>
<b>External Components</b>						
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Patient Programmer	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ388	\$632	277756



Group	Subgroup	Device Name	Sponsor	Billing Code	Benefit	ARTG
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Precision Plus Remote Patient Programmer; Precision Plus with MultiwaveTechnology Remote Patient Programmer	Boston Scientific Australia Pty Ltd	BS106	\$1,354	128681 166929 231196
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Precision Spectra Patient Remote Programmer	Boston Scientific Australia Pty Ltd	BS253	\$1,354	206305 206306
04.05.02 - External Components	04.05.02.01 - Patient Programmer	FreeLink Remote Control Kit	Boston Scientific Australia Pty Ltd	BS325	\$1,354	283694 287237 287738 318330 318331 362974 362991
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Nevro PTRC2300 Patient Remote Control	Emergo Asia Pacific Pty Ltd	ER608	\$1,354	330707
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Surescan MRI Patient programmer	Medtronic Australasia Pty Ltd	MI138	\$1,354	214421
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Intellis Rechargeable Neurostimulation System - PTM Patient Programmer	Medtronic Australasia Pty Ltd	MI276	\$1,354	298760
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Reactiv8 Activator	MAINSTAY MEDICAL (AUSTRALIA) PTY LIMITED	PQ005	\$1,354	327090 <sup>b</sup>
04.05.02 - External Components	04.05.02.01 - Patient Programmer	ANS Spinal Cord Stimulation System (SCS) GENESIS	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ177	\$1,354	106669
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Eon Neurostimulation System	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ183	\$1,354	127127
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Prodigy Patient Programmer	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ348	\$1,354	230778
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Axiom Neurostimulator System - Programmer - Patient	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ355	\$1,354	202322 300051
04.05.02 - External Components	04.05.02.01 - Patient Programmer	Evoke Pocket Console	SALUDA MEDICAL PTY LIMITED	UY007	\$1,354	336570
04.05.02 - External Components	04.05.02.02 - Patient Programmer Antenna	Restore Rechargeable Neurostimulation System	Medtronic Australasia Pty Ltd	MC694	\$161	146936
04.05.02 - External Components	04.05.02.03 - On/Off switching device	Nevro Spinal Cord Stimulation System (SCSS) - Patient Remote Kit	Emergo Asia Pacific Pty Ltd	ER009	\$1,264	185994
04.05.02 - External Components	04.05.02.03 - On/Off switching device	Senza Omnia Patient Remote	Emergo Asia Pacific Pty Ltd	ER536	\$1,264	330708
04.05.02 - External Components	04.05.02.03 - On/Off switching device	Reactiv8 Magnet	MAINSTAY MEDICAL (AUSTRALIA) PTY LIMITED	PQ001	\$1,264	327094 <sup>b</sup>
04.05.02 - External Components	04.05.02.03 - On/Off switching device	ANS Spinal Cord Stimulation System (SCS) GENESIS	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ433	\$1,264	267026 342820
04.05.02 - External Components	04.05.02.04 - Recharger	Precision SCS External Patient Recharger System	Boston Scientific Australia Pty Ltd	BS143	\$1,215	149462 155857 155859 155924

Group	Subgroup	Device Name	Sponsor	Billing Code	Benefit	ARTG
04.05.02 - External Components	04.05.02.04 - Recharger	Nevro Spinal Cord Stimulation System (SCSS) - Charger Kit	Emergo Asia Pacific Pty Ltd	ER008	\$1,215	181182
04.05.02 - External Components	04.05.02.04 - Recharger	Senza Omnia Charger	Emergo Asia Pacific Pty Ltd	ER540	\$1,215	328684
04.05.02 - External Components	04.05.02.04 - Recharger	Medtronic Patient Recharger System	Medtronic Australasia Pty Ltd	MI139	\$1,215	121279
04.05.02 - External Components	04.05.02.04 - Recharger	Intellis Rechargeable Neurostimulation System - RTM Recharger	Medtronic Australasia Pty Ltd	MI277	\$1,215	121279
04.05.02 - External Components	04.05.02.04 - Recharger	Eon Mini Charger	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ342	\$1,215	221544
04.05.02 - External Components	04.05.02.04 - Recharger	Prodigy Charging System	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ349	\$1,215	230779
04.05.02 - External Components	04.05.02.04 - Recharger	Eon Charging System 3726	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ352	\$1,215	233616
04.05.02 - External Components	04.05.02.04 - Recharger	Evoke Charger (AU)	SALUDA MEDICAL PTY LIMITED	UY005	\$1,215	338061
04.05.02 - External Components	04.05.02.05 - External Neurostimulator	Intellis Wireless External Neurostimulator	Medtronic Australasia Pty Ltd	MI280	\$1,083	293256
<b>Leads</b>						
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Medtronic Pisces Quad Leads	Medtronic Australasia Pty Ltd	MC827	\$3,069	137348 <sup>a</sup> 143034 <sup>a</sup> 143035 <sup>a</sup>
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Reactiv8 Percutaneous Lead	MAINSTAY MEDICAL (AUSTRALIA) PTY LIMITED	PQ003	\$3,069	327091 <sup>b</sup>
04.05.03 - Leads	04.05.03.01 - Permanent Lead	ANS Spinal Cord Stimulation System (SCS)	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ162	\$3,069	131944
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Lamitrode S Series Leads	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ186	\$3,069	126076
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Lamitrode S Series Leads	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ187	\$3,069	126076
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Axiom Neurostimulator System - Implant Lead Kit	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ359	\$3,069	301386 301387 333462 333463 202325
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Precision SCS Eight Contact Leads	Boston Scientific Australia Pty Ltd	BS109	\$3,817	128775
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Avista MRI 8 Contact Lead	Boston Scientific Australia Pty Ltd	BS331	\$3,817	287236
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Nevro Spinal Cord Stimulation System (SCSS) - Lead Kit	Emergo Asia Pacific Pty Ltd	ER006	\$3,817	185992
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Surpass-C Surgical Lead	Emergo Asia Pacific Pty Ltd	ER606	\$3,817	368530
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Neurostimulation System - Octad Leads	Medtronic Australasia Pty Ltd	MC690	\$3,817	123243 <sup>a</sup>
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Neurostimulation System - Octad Leads	Medtronic Australasia Pty Ltd	MC710	\$3,817	123241 <sup>a</sup>
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Neurostimulation System - Octad Leads	Medtronic Australasia Pty Ltd	MC711	\$3,817	123243 <sup>a</sup>

Group	Subgroup	Device Name	Sponsor	Billing Code	Benefit	ARTG
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Neurostimulation System - Octad Leads	Medtronic Australasia Pty Ltd	MC712	\$3,817	123243 <sup>a</sup>
04.05.03 - Leads	04.05.03.01 - Permanent Lead	SCS Sub Compact Lead	Medtronic Australasia Pty Ltd	MC740	\$3,817	137079
04.05.03 - Leads	04.05.03.01 - Permanent Lead	SCS Sub Compact Lead	Medtronic Australasia Pty Ltd	MC759	\$3,817	137080
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Vectris Surescan MRI Neurostimulation Leads	Medtronic Australasia Pty Ltd	MI136	\$3,817	214838 214839
04.05.03 - Leads	04.05.03.01 - Permanent Lead	ANS Spinal Cord Stimulation System (SCS)	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ161	\$3,817	132097
04.05.03 - Leads	04.05.03.01 - Permanent Lead	ANS Spinal Cord Stimulation System (SCS)	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ168	\$3,817	126005 126079 126076
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Lamitrode S Series	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ185	\$3,817	126002
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Lamitrode C Series Leads	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ188	\$3,817	126142
04.05.03 - Leads	04.05.03.01 - Permanent Lead	CoverEdge 32 Contact Surgical Leads	Boston Scientific Australia Pty Ltd	BS255	\$11,011	218230
04.05.03 - Leads	04.05.03.01 - Permanent Lead	INFINION Lead	Boston Scientific Australia Pty Ltd	BS356	\$6,895	197909
04.05.03 - Leads	04.05.03.01 - Permanent Lead	ARTISAN, ARTISAN MRI Lead	Boston Scientific Australia Pty Ltd	BS357	\$6,895	163471 308180
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Specify 5-6-5 Surgical Lead	Medtronic Australasia Pty Ltd	MC776	\$6,895	148397
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Specify 2x8 Surgical Lead	Medtronic Australasia Pty Ltd	MC942	\$6,895	163895
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Specify SureScan MRI 5-6-5 Lead Kit	Medtronic Australasia Pty Ltd	MI199	\$6,895	280179
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Specify SureScan MRI 2x8 Surgical Lead Kit	Medtronic Australasia Pty Ltd	MI209	\$6,895	280180
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Lamitrode Lead - Tripole 16C	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ138	\$6,895	155013
04.05.03 - Leads	04.05.03.01 - Permanent Lead	ANS Spinal Cord Stimulation System (SCS)	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ169	\$6,895	126004
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Evoke 12C Percutaneous Lead Kit	SALUDA MEDICAL PTY LIMITED	UY009	\$6,895	336573
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Infinion CX Lead	Boston Scientific Australia Pty Ltd	BS312	\$8,123	275241
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Surpass Surgical Lead	Emergo Asia Pacific Pty Ltd	ER388	\$8,123	284256
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Surpass-C Surgical Lead	Emergo Asia Pacific Pty Ltd	ER607	\$8,123	368530
04.05.03 - Leads	04.05.03.01 - Permanent Lead	Penta Leads	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ231	\$8,123	170450
04.05.03 - Leads	04.05.03.02 - Trial Lead	Precision SCS Lead Blanks	Boston Scientific Australia Pty Ltd	BS118	\$438	156757
04.05.03 - Leads	04.05.03.02 - Trial Lead	Medtronic Vectris Neurostimulation Trial Lead	Medtronic Australasia Pty Ltd	MI137	\$438	219258 219259
<b>Lead Extension</b>						
04.05.04 - Lead Extension	No subgroup	Precision SCS Lead Extensions	Boston Scientific Australia Pty Ltd	BS111	\$1,362	128679
04.05.04 - Lead Extension	No subgroup	Precision Connector M1	Boston Scientific Australia Pty Ltd	BS158	\$1,362	162422
04.05.04 - Lead Extension	No subgroup	Precision SCS Splitter	Boston Scientific Australia Pty Ltd	BS169	\$1,362	167101 167102 197908

Group	Subgroup	Device Name	Sponsor	Billing Code	Benefit	ARTG
04.05.04 - Lead Extension	No subgroup	Precision M8 Adaptor	Boston Scientific Australia Pty Ltd	BS323	\$1,362	281250
04.05.04 - Lead Extension	No subgroup	Nevro Spinal Cord Stimulation System (SCSS) - Lead Extension Kit	Emergo Asia Pacific Pty Ltd	ER007	\$1,362	185993
04.05.04 - Lead Extension	No subgroup	Nevro Spinal Cord Stimulation System (SCSS) - Pocket Adaptor Kit - S8	Emergo Asia Pacific Pty Ltd	ER102	\$1,362	199081
04.05.04 - Lead Extension	No subgroup	Nevro Spinal Cord Stimulation System (SCSS) - Pocket Adaptor Kit - M8	Emergo Asia Pacific Pty Ltd	ER130	\$1,362	204062
04.05.04 - Lead Extension	No subgroup	Quadripolar Stretch-Coil Extensions	Medtronic Australasia Pty Ltd	MC733	\$1,362	239412
04.05.04 - Lead Extension	No subgroup	Quadripolar Stretch-Coil Extensions	Medtronic Australasia Pty Ltd	MC734	\$1,362	239412
04.05.04 - Lead Extension	No subgroup	Pocket Adaptors for Spinal Cord Stimulation	Medtronic Australasia Pty Ltd	MC941	\$1,362	165114
04.05.04 - Lead Extension	No subgroup	Neurostimulation System - Extensions	Medtronic Australasia Pty Ltd	MI445	\$1,362	239412
04.05.04 - Lead Extension	No subgroup	ANS Spinal Cord Stimulation System (SCS)	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ160	\$1,362	126001 126078
04.05.04 - Lead Extension	No subgroup	A127 Lead Extension	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ178	\$1,362	119863
04.05.04 - Lead Extension	No subgroup	Axiom Neurostimulator System - Lead Extension Kit	ABBOTT MEDICAL AUSTRALIA PTY LTD.	SJ358	\$1,362	203096 301410 333448
04.05.04 - Lead Extension	No subgroup	Evoke 12C Lead Extension Kit - 55cm	SALUDA MEDICAL PTY LIMITED	UY004	\$1,362	336571
<b>Accessories</b>						
04.05.05 - Accessories	04.05.05.02 - Plug	Precision SCS IPG Port	Boston Scientific Australia Pty Ltd	BS121	\$152	156761
04.05.05 - Accessories	04.05.05.02 - Plug	Nevro Spinal Cord Stimulation System (SCSS) - IPG Port Plug Kit	Emergo Asia Pacific Pty Ltd	ER042	\$152	190837
04.05.05 - Accessories	04.05.05.02 - Plug	Neurostimulation System - Accessory Kits	Medtronic Australasia Pty Ltd	MC687	\$152	121280
04.05.05 - Accessories	04.05.05.02 - Plug	Medtronic Percutaneous Quad extension	Medtronic Australasia Pty Ltd	MC825	\$152	239412
04.05.05 - Accessories	04.05.05.05 - Connectors and Cables	Medtronic Neurostimulation Screening Cable	Medtronic Australasia Pty Ltd	MI049	\$181	119991
04.05.05 - Accessories	04.05.05.05 - Connectors and Cables	Evoke Lead Adapter Kit	SALUDA MEDICAL PTY LIMITED	UY002	\$181	323488

**Notes:** a Medtronic leads approved for use for both SCS and PNS placement.

b PNS devices, leads and accessories

## Appendix B MBS items

**Table App 2 MBS items for SCS and PNS for the management of pain**

MBS item number	MSB item description	Explanatory note
39129	Peripheral lead or leads, percutaneous placement of, including intraoperative test stimulation, for the management of chronic neuropathic pain (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$641.40 Benefit: 75% = \$481.05	TN.8.241 (Table App 3)
39130	Epidural lead or leads, percutaneous placement of, including intraoperative test stimulation, for the management of chronic neuropathic pain or pain from refractory angina pectoris (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$712.65 Benefit: 75% = \$534.50	TN.8.244 (Table App 3)
39134	Neurostimulator or receiver, subcutaneous placement of, including placement and connection of extension wires to epidural or peripheral nerve electrodes, for the management of chronic neuropathic pain or pain from refractory angina pectoris (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$360.05 Benefit: 75% = \$270.05	TN.8.244 (Table App 3)
39135	Neurostimulator or receiver that was inserted for the management of chronic neuropathic pain or pain from refractory angina pectoris, open surgical removal of, performed in the operating theatre of a hospital (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$168.55 Benefit: 75% = \$126.45	TN.8.244 (Table App 3)
39137	Epidural or peripheral nerve lead that was implanted for the management of chronic neuropathic pain or pain from refractory angina pectoris, open surgical repositioning of, to correct displacement or unsatisfactory positioning, including intraoperative test stimulation, other than a service to which item 39130, 39138 or 39139 applies (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$641.40 Benefit: 75% = \$481.05	TN.8.244 (Table App 3)
39136	Epidural or peripheral nerve lead that was implanted for the management of chronic neuropathic pain or pain from refractory angina pectoris, open surgical removal of, performed in the operating theatre of a hospital (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$174.60 Benefit: 75% = \$130.95	TN.8.244; TN.8.4 (Table App 3)
39138	Peripheral nerve lead or leads, surgical placement of, including intraoperative test stimulation, for the management of chronic neuropathic pain where the leads are intended to remain in situ long term (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$712.65 Benefit: 75% = \$534.50	TN.8.241 (Table App 3)
39139	Epidural lead, surgical placement of one or more of by partial or total laminectomy, including intraoperative test stimulation, for the management of chronic neuropathic pain or pain from refractory angina pectoris (H) Multiple Operation Rule (Anaes.) (Assist.) Fee: \$956.85 Benefit: 75% = \$717.65	TN.8.244 (Table App 3)

**Table App 3 Explanatory Notes associated with MBS items in Table App 2**

Explanatory note	Description
TN.8.241	<p><b>Placement of peripheral nerve leads for the management of chronic intractable neuropathic pain (Items 39129 and 39138)</b></p> <p>Items 39129 and 39138 are for the insertion of leads that are intended to remain in situ long term. Percutaneous Electrical Nerve Stimulation (PENS) is not to be claimed under these items. The use of PENS for the management of chronic pain has not been assessed by the Medical Services Advisory Committee (MSAC) or recommended for public funding. Therefore, PENS procedures for management of chronic pain cannot be billed under the MBS, including items 39129 and 39138. Item 39138 is the appropriate item to claim when surgical lead placement is required for a trial procedure prior to longer term placement. Item 39129 is the appropriate item for the percutaneous placement of leads, including for trial procedures. Items 39129 and 39138 provide for the insertion of one or multiple leads. There is no intention to change current billing practices for these items, e.g. where more than one lead may be billed as part of an episode</p>
TN.8.244	<p><b>Implanted device items</b></p> <p>As with all interventions, implant procedures should be performed in the context of clinical best practice. This is of particular importance given the high cost of the devices. Current clinical best practice for use of these item numbers includes:</p> <ul style="list-style-type: none"> <li>• All procedures being performed in the context of a comprehensive pain management approach with a multidisciplinary team</li> <li>• Patients should be appropriately selected for the procedure, including, but not limited to assessment of physical and psychological function prior to implantation with findings documented in the medical record.</li> <li>• Outcome evaluation pre and post implantation.</li> <li>• Appropriate follow-up and ongoing management of implanted medical devices should be ensured.</li> </ul> <p>Implantable devices require ongoing monitoring and management. If the person providing the implantation service is not the ongoing physician manager of the device, they are responsible for ensuring that appropriate ongoing management has been arranged. Items 39130 and 39139 provide for the insertion of one or multiple leads. There is no intention to change current billing practices for these items, e.g. where more than one lead may be billed as part of an episode. Item 39133 can be billed twice per attendance where services are separate procedures. Accompanying text is required for these claims such as one item is for the removal of an infusion pump and one item is for the removal or repositioning of a spinal catheter.</p>

Note: TN 8.4 relates to aftercare (post-operative treatment) and is not shown

## Appendix C Methodology

### C.1 Comparative clinical effectiveness

#### C.1.1 Targeted evidence scan

A rapid search of peer-reviewed scientific literature and grey literature was conducted to supplement documents provided by DoHAC, sponsors, and stakeholders. A pragmatic approach was taken with a focus on identifying the most comprehensive, high quality, and recent SRs that addressed the study question, and supplementing this with additional studies if necessary. Details of the search strategy are provided in Section 3.1.

**Table App 4 Search strategy to identify evidence on SCS**

Source of information	Database/website	Data limit	Search terms
Electronic databases	Epistemonikos ( <a href="https://www.epistemonikos.org">https://www.epistemonikos.org</a> )	2018-present	Spinal cord stimulation
	Cochrane library (Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials)		Spinal cord stimulator
HTA websites	International Network of Agencies for Health Technology Assessment	No limit	Spinal cord stimulation
<i>Australia</i>	Centre for Clinical Effectiveness, Monash University		Spinal cord stimulator
	Centre for Health Economics, Monash University		SCS
<i>Canada</i>	Alberta Heritage Foundation for Medical Research (AHFMR)		Neurostimulator
	Alberta Institute of Health Economics		Neurostimulation
	The Canadian Association for Health Services and Policy Research (CAHSPR)		Neuromodulation
	Centre for Health Economics and Policy Analysis (CHEPA), McMaster University		
	Centre for Health Services and Policy Research (CHSPR), University of British Columbia		
	Institute for Clinical and Evaluative Studies (ICES)		
	Saskatchewan Health Quality Council (Canada)		
<i>Denmark</i>	Danish National Institute Of Public Health		
<i>Finland</i>	Finnish National Institute for Health and Welfare		
<i>Germany</i>	German Institute for Medical Documentation and Information (DIMDI) / HTA		
	Institute for Quality and Efficiency in Health Care (IQWiG)		
<i>The Netherlands</i>	Health Council of the Netherlands (Gezondheidsraad)		
<i>New Zealand</i>	New Zealand Health Technology Assessment (NZHTA)		
<i>Norway</i>	Norwegian Institute of Public Health, Norwegian Knowledge Centre for the Health Services		
<i>Spain</i>	Andalusian Agency for Health Technology Assessment (Spain)		
	Catalan Agency for Health Technology Assessment (CAHTA)		
<i>Sweden</i>	Center for Medical Health Technology Assessment		
	Swedish Council on Technology Assessment in Health Care (SBU)		
<i>UK</i>	National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)		
	NHS Quality Improvement Scotland		
	The European Information Network on New and Changing Health Technologies		
	University of York NHS Centre for Reviews and Dissemination (NHS CRD)		
<i>USA</i>	Agency for Healthcare Research and Quality (AHRQ)		
	Harvard School of Public Health		
	Institute for Clinical and Economic Review		

Source of information	Database/website	Data limit	Search terms
	Minnesota Department of Health (US)		
	National Information Centre of Health Services Research and Health Care Technology (US)		
	U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (Tec)		
	Veteran's Affairs Research and Development Technology Assessment Program (US)		
Clinical trials registries	ClinicalTrials.gov	No limit	Spinal cord stimulation
	Australian New Zealand Clinical Trials Registry		Spinal cord stimulator

Abbreviations: HTA, health technology assessment; SCS, spinal cord stimulation

The search of the Epistemonikos database identified 224 potentially relevant systematic reviews; after screening the titles and abstracts, 27 potentially relevant studies were identified. A further four HTAs were identified in the search. No additional relevant studies were identified from documents supplied by DoHAC, including a review of the TGA literature search. The potentially relevant studies were screened in full text.

O'Connell (2021) published by the Cochrane Collaboration was identified as the most recent, applicable, and comprehensive evidence source. During preparation of this review, a second study published by the Cochrane Collaboration (Traeger 2023) was published. These two SRs were selected as key studies for this review.

The search of clinical trials registries identified nine ongoing RCTs that are relevant to this review (Table App 5). An additional 18 ongoing RCTs were identified in the O'Connell (2021) and Traeger (2023) Cochrane reviews (Table App 6).



**Table App 5 Ongoing RCTs identified in independent search of clinical trials registries**

Registry ID Study title	Population	Interventions	Key outcomes	Study start date & expected completion	Included in O'Connell	Included in Traegar
NCT03740763 Spinal Cord Stimulation and Physiotherapy for Treatment of Neuropathic Pain (SCS-PHYSIO)	<u>Estimated enrolment:</u> N=160 participants <u>Location:</u> Sweden <u>Inclusion:</u> 18-99 yrs old; neuropathic pain >6 mo; pain intensity ≥6 according to NRS; known cause of the pain; neuroanatomical correlation to the pain; ≥50% of the painful area is to be treated with SCS; patient has a physical and psychological health status that allows the patient to participate in physiotherapy and undergo SCS implantation	<u>Device 1:</u> SCS <u>Device 2:</u> physiotherapy	<u>Primary:</u> pain intensity according to NRS <u>Secondary:</u> pain intensity according to NRS; HRQoL according to SF36, EQ-5D; physical activity; return to work; days of sick-leave; medical consumption; patient treatment satisfaction according to NRS	<u>Study start date:</u> 09 May 2018 <u>Primary completion date:</u> May 2023 <u>Study completion date:</u> May 2025	✓	
NCT04676022 SCS as an Option for Chronic Low Back and/or Leg Pain Instead of Surgery (SOLIS)	<u>Estimated enrolment:</u> N=241 participants <u>Location:</u> USA <u>Inclusion:</u> ≥22 yrs old; ≥6 mo CLBP with/without leg pain; received ≥90 days of documented pain management care prior to screening to address the primary pain complaint; not pregnant	<u>Intervention:</u> WaveWriter <u>Comparator:</u> conventional medical management	<u>Primary:</u> responder rate <sup>a</sup>	<u>Study start date:</u> 26 March 2021 <u>Primary completion date:</u> 25 August 2022 <u>Study completion date:</u> December 2025	✓	✓
NCT03876054 Long-Term Real-World Outcomes Study on Patients Implanted With a Neurostimulator (REALITY)	<u>Estimated enrolment:</u> 2000 participants <u>Location:</u> USA, UK, Australia, Belgium, Germany, Italy, Netherlands, Spain, Switzerland <u>Inclusion:</u> ≥18 yrs old; written informed consent prior to any clinical investigation related procedure; scheduled to have an Abbott neurostimulation system implanted within 60 days of baseline; baseline pain NRS ≥6	<u>Device 1:</u> SCS <u>Device 2:</u> DRGS	<u>Primary:</u> rate of device and procedure-related AEs, deaths and device deficiencies <sup>a</sup>	<u>Study start date:</u> 13 March 2019 <u>Primary completion date:</u> June 2029 <u>Study completion date:</u> December 2029		
NCT05466110 Spinal Cord Stimulation Versus Instrumentation for FBSS (PROMISE)	<u>Estimated enrolment:</u> 84 participants <u>Location:</u> Germany <u>Inclusion:</u> ≥18 yrs old; symptomatic degenerative disc disease with LBP as a predominant symptom for at least 6 mo following previous surgery for disc herniation; ≥21 ODI score	<u>Intervention:</u> SCS (WaveWriter Alpha) <u>Comparator:</u> spinal fusion surgery	<u>Primary outcomes:</u> ODI <u>Secondary outcomes:</u> AEs; SF36; EQ 5D; hospital LOS; cross-over rates; pain medication	<u>Study start date:</u> November 2022 <u>Primary completion date:</u> November 2024 <u>Study completion date:</u> May 2025		
NCT04479787 Spinal Cord Stimulation vs. Medical Management for Low Back Pain (DISTINCT) <i>Moeschler 2021</i>	<u>Actual enrolment:</u> 270 participants <u>Location:</u> USA <u>Inclusion:</u> ≥18 yrs old; chronic (at least 6 mo), refractory axial low back pain with a neuropathic component and is not a candidate for spine surgery; back pain for ≥ 6 months inadequately responsive to supervised conservative care; not had spine surgery for back or leg pain; low back pain ≥ 6 on NRS; ODI score of ≥ 30%	<u>Intervention:</u> SCS (Proclaim XR IPG) <u>Comparator:</u> CMM	<u>Primary outcomes:</u> Improvement in pain, defined as a ≥ 50% decrease on NRS at 6 mo <u>Secondary outcomes:</u> Change in ODI from baseline, and the percentage of change in NRS from baseline at 6 mo	<u>Study start date:</u> July 2020 <u>Primary completion date:</u> August 2022 <u>Study completion date:</u> January 2024	✓	✓

Registry ID Study title	Population	Interventions	Key outcomes	Study start date & expected completion	Included in O'Connell	Included in Traegar
ACTRN12620000720910 An evaluation of spinal cord stimulation for the treatment of chronic pain, also its effect on mood, sleep, physical activity and analgesic medicine requirements.	<u>Target sample size:</u> 10 <u>Location:</u> Australia <u>Inclusion:</u> 18-80 yrs; implants with BurstDR electrical stimulation; report significant pain relief (defined as average pain less than 3/10 from their stimulator); minimal requirements for analgesic medication (defined as less than 20 Morphine Equivalent Dose (MEq)); without any accompanying sensation from electrical stimulation	<u>Intervention:</u> stimulation on <u>Comparator:</u> stimulation off	<u>Primary outcomes:</u> assessment of pain using BPI; assessment of sleep quality using Sleep Diary; consumption of analgesic medication using daily medication diary <u>Secondary outcomes:</u> patient activity using a pedometer; assessment of behavioural signs of pain using Pain Behavioural Score; assessment of pressure-pain using a pressure sensor applied at 100g/sec to the patients forehead until patient reports pain. Patients will also rate sharpness evoked by the 1 sec application of a spring-loaded metal pin at a force of 40g followed by 5 further applications of the pin with rests of 1 sec between each application; patient stress and anxiety levels using DASS-21 and Pain Catastrophizing Scale	<u>Study start date:</u> September 2020 <u>Study completion date:</u> October 2023	✓	✓
Ahmadi 2021 Efficacy of different spinal cord stimulation paradigms for the treatment of chronic neuropathic pain (PARS-trial)	<u>Estimated enrolment:</u> 2-3 patients/year at 10 centres <u>Location:</u> Germany <u>Inclusion:</u> ≥18 yrs old; patients suffering from intractable neuropathic pain; already implanted with a wireless SCS device; found eligible for SCS therapy according to the German guidelines; pain symptoms persisting for at least 6 mo	<u>Intervention:</u> SCS (burst, 1 kHz, 1.499 kHz, placebo) <u>Comparator:</u> SCS (burst, 1 kHz, 1.499 kHz, placebo)	<u>Primary outcomes:</u> level of pain measured on the VAS after 120 hrs of SCS <u>Secondary outcomes:</u> pain quality questionnaire (painDETECT); anxiety perception (HADS-D); physical restriction (ODI)	<u>Study start date:</u> NR <u>Study completion date:</u> 2 years	✓	✓
ISRCTN10663814 Comparison of spinal cord stimulation in combination with standard pain treatment versus standard pain treatment only in patients with intractable chronic back pain without previous history of spine surgery	<u>Final enrolment:</u> 115 participants <u>Location:</u> Belgium, Germany, Netherlands, Spain <u>Inclusion:</u> ≥18 yrs old; chronic, refractory axial low back pain with or without lower limb pain with a neuropathic component; not eligible for spine surgery; average back pain intensity ≥ 6.0 cm on the 10.0 cm VAS; stable pain medication regime for at least 30 days prior	<u>Intervention:</u> DTM SCS + CMM <u>Comparator:</u> CMM	<u>Primary outcomes:</u> Individual responder rate measured using VAS (as defined by at least a 50% reduction in pain) at 6 mo <u>Secondary outcomes:</u> successful back pain relief measured using VAS at 1, 3, 6, 9, 12, 18 and 24 mo; percentage of patients who experience at least 50% reduction in pain intensity measured using the VAS at 1, 3, 6, 9, 12, 18 and 24 mo; back pain intensity measured using VAS at baseline, 1, 3, 6, 9, 12, 18 and 24 mo	<u>Study start date:</u> January 2020 <u>Study completion date:</u> March 2024	✓	✓

Registry ID Study title	Population	Interventions	Key outcomes	Study start date & expected completion	Included in O'Connell	Included in Traegar
NCT03718325 Burst Spinal Cord Stimulation (Burst-SCS) Study	<u>Estimated enrolment:</u> 20 participants <u>Location:</u> USA <u>Inclusion:</u> chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with any of the following: failed back surgery syndrome and intractable low back and leg pain, and for whom Burst-SCS has been recommended as a treatment option	<u>Intervention:</u> Burst SCS <u>Comparator:</u> Sham	<u>Primary outcomes:</u> change in VAS score at 2 wks <u>Secondary outcomes:</u> change in SFMPQ score at 2 wks; change in general PDI score at 2 wks; change in BPI-SF at 2 wks; MBM at 2 wks; FSQ at 2 wks	<u>Study start date:</u> March 2019 <u>Primary completion date:</u> June 2023 <u>Study completion date:</u> June 2023	✓	✓
NCT04915157 Efficacy of Spinal Cord Stimulation in Patients With Refractory Angina Pectoris (SCRAP)	<u>Estimated enrolment:</u> 72 <u>Location:</u> The Netherlands <u>Inclusion:</u> RAP <sup>b</sup> ; proven ischaemia <sup>c</sup> ; no revascularisation (PCI and/or CABG) performed between ischaemia testing and study inclusion; age >18 yrs.	<u>Intervention:</u> high density stimulation <u>Comparator:</u> no stimulation	<u>Primary outcomes:</u> myocardial ischaemia <u>Secondary outcomes:</u> patient conditions; frequency of angina pectoris attacks; severity of angina pectoris attacks; grading of angina pectoris; frequency of short-acting nitroglycerin use; QoL outcome; hospital admissions due to acute coronary syndrome; revascularisation; emergency room visits due to angina pectoris; cardiovascular mortality; changes in regional and global myocardial blood flow and myocardial flow reserve <sup>a</sup>	<u>Study start date:</u> 21 December 2021 <u>Primary completion date:</u> June 2024 <u>Study completion date:</u> June 2025		

Abbreviations: AEs, adverse events; BPI-SF, Brief Pain Inventory; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CLBP, chronic low back pain; CMM, conventional medical management; cm, centimetres; DASS, Depression, Anxiety and Stress Scale; DRGS, dorsal root ganglion stimulation; EQ, EuroQol; FBSS, failed back surgery syndrome; FFR, fractional flow reserve; FSQ, Fibromyalgia Survey Questionnaire; HADS-D, Hospital And Anxiety Depression Scale; hrs, hours; HRQoL, health-related quality of life; kHz, kilohertz; LBP, low back pain; LOS, length of stay; MBM, Michigan Body Map; mo, months; MRI, magnetic resonance imaging; N, population; NR, not reported; NRS, numeric rating scale; ODI, Oswestry Disability Index; PCI, percutaneous coronary intervention; PDI, General Pain Disability Index; PET, positron emission tomography; RAP, refractory angina pectoris; SCS, spinal cord stimulation; SFMPQ, Short Form McGill Pain Questionnaire; SF36, Short Form 36; VAS, visual analogue scale; vs, versus; yrs, years

**a** Trial also includes a number of "other outcomes"

**b** Stable angina pectoris CCS class III or IV, with a minimum of 5 episodes of angina pectoris over the course of one week, during a minimum period of three months prior to screening; Coronary angiogram (CAG) performed within the last 12 months showing significant coronary artery disease defined as at least one coronary artery stenosis of >75% or 50 - 75% with proven ischaemia (see below), not suitable for revascularisation. Confirmed by one (or two in case of doubt) interventional cardiologist based on CAG images; Optimal anti-anginal medication. Patients should at least use the maximal tolerable dose of a b-blocker, calcium channel blocker and short- and/or long-acting nitrate. If the patient doesn't use one of these groups of medication the reason (side-effects) should be clear.

**c** MIBI-SPECT: summed stress score (SSS) of at least 1, in combination with summed difference score (SDS) of at least 1 (1-4 mild ischaemia, > 4 moderate to severe ischaemia); FFR: < 0.80, with no intervention options (determined by interventional cardiologist); MRI perfusion: ≥ 1 segment of subendocardial hypoperfusion during stress perfusion, not present at rest and no matching fibrosis (using 16 segment AHA heart model); PET: Semi-quantitative measurement: SSS score of at least 1, in combination with SDS score of at least 1 (1-4 mild ischaemia, > 4 moderate to severe ischaemia). Quantitative measurement: reduced myocardial perfusion reserve

Note: Trials with a past estimated completion date have not been included

**Table App 6 Additional ongoing RCTs identified in the Cochrane reviews (O'Connell 2021 and Traeger 2023)**

RCT identifier	Study ID/ Registry ID	Title	Included in O'Connell	Included in Traeger
	ChiCTR-IOR-17012289	A randomized controlled study of spinal cord electrical stimulation in the treatment of pain in patients with diabetic foot.	✓	
CITRIP	Lu 2020	Spinal cord stimulation for chronic intractable trunk or limb pain: study protocol for a Chinese multicenter randomized withdrawal trial	✓	
	DRKS00022557	Effect of stimulation frequency in dorsal root ganglion stimulation (DRG Stimulation)	✓	
MODULATE- LBP	Al-Kaisy 2020	Multicentre, double-blind, randomised, sham-controlled trial of 10 khz high-frequency spinal cord stimulation for chronic neuropathic low back pain	✓	✓
	NCT03546738	Spinal cord Burst stimulation for chronic radicular pain following lumbar spine surgery: a randomized double-blind sham-controlled crossover trial	✓	
	NCT03733886	A randomised sham-controlled double-blinded study of burst spinal cord stimulation for chronic peripheral neuropathic pain	✓	
	NCT04039633	Spinal cord stimulation for refractory pain in erythromelalgia	✓	
	NCT04894734	Spinal cord stimulation (SCS) for spinal cord injury (SCI)	✓	
PANACEA		Prospective, randomised, crossover, controlled, feasibility study to assess the efficacy of BurstDR spinal cord stimulation (SCS) as a treatment for persistent abdominal refractory visceral pain secondary to chronic pancreatitis:trial	✓	
PET-SCS	NCT03419312	PET patterns, biomarkers and outcome in treated FBSS patients	✓	✓
SENZA-NSRBP	Al-Kaisy 2018	Medical management versus 10 kHz spinal cord stimulation and medical management for the treatment of nonsurgical back pain	✓	
	Patel 2021	High-frequency spinal cord stimulation at 10 kHz for the treatment of nonsurgical refractory back pain: design of a pragmatic, multicenter, randomized controlled trial	✓	
	Reiters 2019	High Frequency Spinal Cord Stimulation (HFSCS) at 10 kHz plus Conventional Medical Management (CMM) versus conventional medical management alone for the treatment of non-surgical back pain	✓	✓
TSUNAMI DRG		A European, prospective, multi-center, double-blind, randomized, controlled, clinical trial investigating the effects of high frequency wireless spinal cord stimulation (SCS) over exiting nerve roots in the treatment of chronic back pain	✓	
	ISRCTN33292457	Senza spinal cord stimulation system for the treatment of chronic back and leg pain in failed back surgery syndrome (FBSS) patients		✓
	NCT03462147	Efficacy of spinal cord stimulation in patients with a failed back surgery syndrome		✓
	NCT03858790	Efficacy and safety of spinal cord stimulation in patients with chronic intractable pain		✓
	NCT04732325	Sensory testing of multiple forms of spinal cord stimulation for pain		✓

Abbreviations: FBSS, failed back surgery syndrome; RCT, randomised controlled trial

## C.1.2 Studies from stakeholder submissions

To supplement the evidence scan and allow for a broader overview of the available evidence, the 18 stakeholder submissions were reviewed for relevant publications that addressed the research questions for this PLR. The publications provided by stakeholders were combined with studies from the two Cochrane reviews (O’Connell 2021 and Traeger 2023), from which a total of 255 publications relating to SCS have been identified by this report and are described below.

### 1. Cochrane Review studies (incl & excl) and stakeholder-provided follow-up publications

- 67 RCT publications reporting on the 20 RCTs included across the two Cochrane reviews – these encompass a number of follow-up studies presenting analyses that may or may not be comparative (overview in Table App 7; list of studies in Table App 8)
- 38 publications specifically excluded from either of the two Cochrane reviews (23 RCT publications and 15 other publications, including one non-randomised comparative cohort study) (Table App 9)
- An additional four publications from stakeholder submissions reporting on three RCTs that were included in either of the Cochrane reviews (Table App 10)
- An additional seven RCT publications from stakeholder submissions reporting on five RCTs that were excluded by either of the Cochrane reviews (Table App 11)

### 2. Stakeholder-provided publications for RCTs not listed in Cochrane reviews

- An additional 13 publications from stakeholder submissions reporting on eight novel RCTs not listed in either Cochrane Review (Table App 12)

### 3. Other stakeholder-provided publications

- An additional 126 non-RCT publications included in submissions from the 18 stakeholders, including the following study and publication types:
  - Non-randomised comparative cohort studies (n=5)
  - Non-comparative cohort studies, including on/off studies (n=55) (Table App 13)
  - SRs (n=13) and meta-analyses (n=4) (Table App 14)
  - Safety studies and reviews (n=8) (Table App 15)
  - Economic and costing studies and reports (n=23) (Table App 16)
  - Studies of clinical longevity (n=1) (Table App 17)
  - Predicted MRI requirement rates (n=1) (Table App 18)
  - Patient selection studies (n=4) (Table App 19)
  - Technical studies, e.g., lead placement, ECAP estimation schemes, dosing studies (n=9) (Table App 20)
  - Critiques and position statements (n=3) (Table App 21).

**Table App 7 RCTs included in either the O'Connell 2021 or Traeger 2023 Cochrane reviews**

RCT identifier	Trial no.	O'Connell 2021	Traeger 2023	Number of study publications
De Ridder 2013		✓	✓	2
de Vos 2014	ISRCTN03269533	✓		4
Eisenberg 2015			✓	1
Eldabe 2021		✓	✓	2
Hara 2022	NCT03546738		✓	1
<b>NSRBP-RCT</b> (Kapural 2022)	SRCTN87648175 & NCT03680846		✓	3
Kemler 2000		✓		4
Kriek 2017 <sup>a</sup>	ISRCTN36655259	✓		3
Lind 2015		✓		2
Perruchoud 2013		✓	✓	1
<b>PROCESS</b>	ISRCTN77527324	✓	✓	11
<b>PROMISE</b>		✓	✓	7
Schu 2014		✓	✓	3
<b>SCS Frequency Study</b> (Al-Kaisy 2018)	NCT01750229	✓	✓	3
<b>SENZA-PDN</b>		✓		13
Slangen 2014		✓		2
Sokal 2020		✓	✓	2
Sweet 2016	NCT05283863		✓	1
Tjepkema-Cloostermans 2016		✓		1
Wolter 2012 <sup>b</sup>			✓	1

Abbreviations: no, number; RCT, randomised controlled trial; SCS, spinal cord stimulation

**a** Included in O'Connell 2021 but excluded from Traeger 2023

**b** Included in Traeger 2023 but excluded from O'Connell 2021

**Table App 8 Study publications for RCTs included in either the O’Connell 2021 or Traeger 2023 Cochrane reviews**

RCT Identifier	Study ID	Title
<i>De Ridder 2013</i>	De Ridder 2013	Burst spinal cord stimulation for limb and back pain
	De Ridder 2016	Burst and tonic spinal cord stimulation: Different and common brain mechanisms
<i>de Vos 2014</i> ISRCTN03269533	De Vos 2011	Spinal cord stimulation in patients with diabetic neuropathic pain
	De Vos 2014	Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial
	Duarte 2016	Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation
	Vos 2013	Spinal cord stimulation in patients with painful diabetic neuropathy
<i>Eisenberg 2015</i>	Eisenberg 2015	Spinal cord stimulation attenuates temporal summation in patients with neuropathic pain
<i>Eldabe 2021</i>	Eldabe 2021	Analgesic Efficacy of “Burst” and Tonic (500 Hz) Spinal Cord Stimulation Patterns: A Randomized Placebo-Controlled Crossover Study
	Tariq 2020	Analgesic efficacy of “burst” and tonic (500 Hz) spinal cord stimulation patterns: A randomised placebo-controlled study
<i>Hara 2022</i> NCT03546738	Hara 2022	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
<i>Kemler 2000</i>	Kemler 2000	Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy
	Kemler 2002	Economic evaluation of spinal cord stimulation for chronic reflex sympathetic dystrophy
	Kemler 2004	The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years’ follow-up of the randomized controlled trial
	Kemler 2008	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
<i>Kriek 2017</i> ISRCTN36655259	Kriek 2014	High frequency and burst spinal cord stimulations in patients with complex regional pain syndrome: A randomized placebo controlled trial
	Kriek 2015	Comparison of tonic spinal cord stimulation, high-frequency and burst stimulation in patients with complex regional pain syndrome: a double-blind, randomised placebo controlled trial
	Kriek 2017	Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial
<i>Lind 2015</i>	Hellström 2013	Spinal cord stimulation in the irritable bowel syndrome-a randomized cross-over trial
	Lind 2015	Therapeutic value of spinal cord stimulation in irritable bowel syndrome: a randomized crossover pilot study
<b>NSRBP-RCT</b> ISRCTN87648175/ NCT03680846	Kapural 2022	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
	Patel 2021	High-Frequency Spinal Cord Stimulation at 10 kHz for the Treatment of Nonsurgical Refractory Back Pain: Design of a Pragmatic, Multicenter, Randomized Controlled Trial
	Province-Azalde 2019	Taking spinal cord stimulation beyond failed back surgery syndrome: Design of a multicenter RCT
<i>Perruchoud 2013</i>	Perruchoud 2013	Analgesic efficacy of high-frequency spinal cord stimulation: A randomized double-blind placebo-controlled study

RCT Identifier	Study ID	Title	
<b>PROCESS</b>	Eldabe 2009	Function and quality of life in failed back surgery syndrome patients following spinal cord stimulation and conventional medical management	
	ISRCTN77527324	Eldabe 2009	Pain in failed back surgery syndrome patients following spinal cord stimulation and conventional medical management
		Eldabe 2010	An analysis of the components of pain, function, and health-related quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management
		Kumar 2005	Spinal Cord Stimulation vs. Conventional Medical Management: A Prospective, Randomized, Controlled, Multicenter Study of Patients with Failed Back Surgery Syndrome (PROCESS Study)
		Kumar 2007	Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome
		Kumar 2008	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
		Kumar 2009	Changes in pain, function and quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management
		Kumar 2010	Pain outcomes in failed back surgery syndrome patients following spinal cord stimulation and conventional medical management
		Kumar 2010	Function and health-related quality of life in failed back surgery syndrome patients following spinal cord stimulation and conventional medical management
		Loeser 2008	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: Commentary
		Manca 2008	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)
		<b>PROMISE</b>	North 2018
North 2020	Postoperative Infections Associated With Prolonged Spinal Cord Stimulation Trial Duration (PROMISE RCT)		
Rigoard 2013	Spinal cord stimulation for predominant low back pain in failed back surgery syndrome: Design and enrollment of an international multicenter randomized controlled trial (promise study)		
Rigoard 2013	Spinal cord stimulation for predominant low back pain in failed back surgery syndrome: Study protocol for an international multicenter randomized controlled trial (PROMISE study)		
Rigoard 2017	Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: An international multicenter randomized trial (PROMISE study)		
Rigoard 2018	Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: 12-month results of an international multicenter randomized trial (PROMISE Study)		
Rigoard 2019	Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: A multicenter randomized controlled trial		
<i>Schu 2014</i>	Schu 2014		Burst or tonic stimulation? first results of a placebo controlled, doubled blinded, randomized study for the treatment of fbss patients
	Schu 2014	A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome	
	Vesper 2017	Burst or tonic stimulation? results of a placebo controlled, double blinded, randomized study for the treatment of fbss patients-3y follow-up	



RCT Identifier	Study ID	Title
<b>SCS Frequency Study</b> (Al-Kaisy 2018) NCT01750229	Al-Kaisy 2016	Spinal cord stimulation study evaluating role of higher frequencies (SCS frequency study) (10524)
	Al-Kaisy 2017	Subject therapy preference post randomized phase in a spinal cord stimulation study using higher frequencies
	Al-Kaisy 2018	Prospective, Randomized, Sham-Control, Double Blind, Crossover Trial of Subthreshold Spinal Cord Stimulation at Various Kilohertz Frequencies in Subjects Suffering From Failed Back Surgery Syndrome (SCS Frequency Study)
<b>SENZA-PDN</b>	Argoff 2018	High frequency spinal cord stimulation (HF-SCS) at 10 kHz for the treatment of neuropathic limb pain from painful diabetic neuropathy
	Argoff 2018	A prospective, randomized, controlled trial of high frequency spinal cord stimulation for the treatment of neuropathic limb pain from painful diabetic neuropathy: The senza-pdn protocol
	Mekhail 2020	High-frequency spinal cord stimulation at 10 kHz for the treatment of painful diabetic neuropathy: design of a multicenter, randomized controlled trial (SENZA-PDN)
	Petersen 2020	10 kHz Spinal Cord Stimulation for Treatment of Painful Diabetic Neuropathy-A Multicenter Randomized Controlled Trial (1612)
	Petersen 2020	Neuromodulation for treatment of painful diabetic neuropathy: A multicentre randomised controlled trial
	Petersen 2020	10 kHz spinal cord stimulation for treatment of painful diabetic neuropathy-a multicenter randomized controlled trial
	Petersen 2020	10 kHz spinal cord stimulation for treatment of painful diabetic neuropathy-a multicenter randomized controlled trial
	Petersen 2020	10 khz spinal cord stimulation for treatment of painful diabetic neuropathy-a multicenter randomized controlled trial
	Petersen 2020	Neuromodulation for treatment of painful diabetic neuropathy - A multicenter randomized controlled trial comparing 10 khz spinal cord stimulation to conventional medical management
	Petersen 2020	10 kHz spinal cord stimulation for treatment of painful diabetic neuropathy: A multicenter randomized controlled trial
	Petersen 2020	Neuromodulation for treatment of painful diabetic neuropathy: A multicenter randomized controlled trial
	Petersen 2020	10 kHz Spinal Cord Stimulation for Treatment of Painful Diabetic Neuropathy -A Multicenter Randomized Controlled Trial
	Petersen 2021	Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial
<i>Slangen 2014</i>	Slangen 2014	Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial
	Slangen 2017	A Trial-Based Economic Evaluation Comparing Spinal Cord Stimulation With Best Medical Treatment in Painful Diabetic Peripheral Neuropathy
<i>Sokal 2020</i>	Malukiewicz 2019	Comparison of tonic, burst and high frequency spinal cord stimulation in chronic pain syndromes: A double-blind, randomised, cross-over, placebo controlled trial
	Sokal 2020	Sub-perception and supra-perception spinal cord stimulation in chronic pain syndrome: A randomized, semi-double-blind, crossover, placebo-controlled trial
<i>Sweet 2016</i> NCT05283863	Sweet 2016	Paresthesia-Free High-Density Spinal Cord Stimulation for Postlaminectomy Syndrome in a Prescreened Population: A Prospective Case Series
<i>Tjepkema-Cloostermans 2016</i>	Tjepkema-Cloostermans 2016	Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation
<i>Wolter 2012</i>	Wolter 2012	Effects of sub-perception threshold spinal cord stimulation in neuropathic pain: a randomized controlled double-blind crossover study

Abbreviations: FBSS, failed back surgery syndrome; HF-SCS, high frequency spinal cord stimulation; Hz, hertz; kHz, kilohertz; RCT, randomized controlled trial; SCS, spinal cord stimulation; y, year

**Table App 9 Publications excluded from O’Connell 2021 or Traeger 2023 Cochrane reviews**

Study ID RCT identifier	Title	Reason for exclusion	O’Connell 2021	Traeger 2023
<b>RCT publications excluded from either Cochrane Review and NOT included in the other Cochrane Review (n=24)</b>				
Amirdelfan 2019  <b>NCT03320863</b>	Non-invasive high-frequency impulse neuromodulation for treatment of chronic back pain: A multicenter, randomized, sham-controlled trial	Not SCS		x
Andersen 2009	The effect of electrical stimulation on lumbar spinal fusion in older patients: A randomized, controlled, multi-center trial: Part 2: Fusion rates	Not SCS		x
Billot 2020  <b>MULTIWAVE NCT03014583</b>	Comparison of conventional, burst and high-frequency spinal cord stimulation on pain relief in refractory failed back surgery syndrome patients: study protocol for a prospective randomized double-blinded cross-over trial (MULTIWAVE study)	No placebo, sham or CMM comparator		x
De Andres 2017	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	No placebo, sham or CMM comparator		x
Deer 2015  <b>ACCURATE</b>	A prospective, randomized, multi-center, controlled clinical trial to assess the safety and efficacy of the spinal modulation Axium® neurostimulation system in the treatment of chronic pain (Accurate Trial): Trial design	No placebo, sham or CMM comparator		x
Deer 2018  <b>SUNBURST</b>	Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform	No placebo, sham or CMM comparator		x
Eldabe 2020  <b>TRIAL-STIM</b>	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	No placebo, sham or CMM comparator		x
Falowski 2019	Nonawake vs awake placement of spinal cord stimulators: A prospective, multicenter study comparing safety and efficacy	Not a comparison of interest [lead placement technique]	x	
Gilligan 2020  <b>ReActiv8-B NCT02577354</b>	Restorative neurostimulation for refractory mechanical chronic low back pain - Results of a randomized active sham controlled trial	Not SCS	x	
Kapural 2015  <b>SENZA-RCT</b>	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	No placebo, sham or CMM comparator		x
Kemler 2001	Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: A randomized trial	Wrong outcomes	x	
Kufakwaro 2012	Neuromodulation of dorsal root ganglion: A comparative study to assess efficacy of pulsed-radiofrequency and neurostimulation in treatment of neuropathic pain	Wrong intervention: DRGS [in scope for this report]	x	
Liu 2020	Clinical study of spinal cord stimulation and pulsed radiofrequency for management of herpes zoster-related pain persisting beyond acute phase in elderly patients	Wrong comparator (pulsed radiofrequency)	x	
Liu 2021	The effect of short-term spinal cord electrical stimulation on patients with postherpetic neuralgia and its effect on sleep quality	Wrong comparator (nerve block)	x	
Meier 2015	Effect of spinal cord stimulation on sensory characteristics: A randomized, blinded crossover study	Treatment period not clinically applicable (O’Connell) Wrong population (Traeger)	x	x
Mekhail 2020	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	Wrong comparator (closed loop SCS) (Traeger)		x
North 1994	A prospective, randomized study of spinal cord stimulation versus reoperation for failed back surgery syndrome: Initial results	Comparator = surgery		x
North 2005	Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: A randomized, controlled trial	Comparator = surgery		x

Study ID RCT identifier	Title	Reason for exclusion	O'Connell 2021	Traeger 2023
North 2020 <b>WHISPER</b> <b>NCT02314000</b>	Outcomes of a Multicenter, Prospective, Crossover, Randomized Controlled Trial Evaluating Subperception Spinal Cord Stimulation at ≤1.2 kHz in Previously Implanted Subjects	No placebo, sham or CMM comparator		×
Roulaud 2015 <b>ESTIMET</b> <b>NCT01628237</b>	Multicolumn spinal cord stimulation for significant low back pain in failed back surgery syndrome: Design of a national, multicentre, randomized, controlled health economics trial (ESTIMET Study)	No placebo, sham or CMM comparator		×
Thomson 2018 <b>PROCO</b>	Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial	No placebo, sham or CMM comparator		×
Vesper 2017	Therapeutic efficacy of burstdr™ microdosing in treatment of chronic pain	No placebo, sham or CMM comparator <sup>a</sup>		×
Vesper 2019	Burst SCS Microdosing Is as Efficacious as Standard Burst SCS in Treating Chronic Back and Leg Pain: Results From a Randomized Controlled Trial	No placebo, sham or CMM comparator <sup>a</sup>		×
<b>Other publication types excluded from the Cochrane reviews (n=14)</b>				
Alo 2016	Commens [on Deer Prospective, multicenter, randomized, double-blinded, partial crossover study to assess the safety and efficacy of the novel neuromodulation system in the treatment of patients with chronic pain of peripheral nerve origin	Commentary <sup>b</sup>	×	
Annemans 2014	Cost effectiveness of a novel 10 khz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS)	Economic analysis performed post hoc and independent of RCT	×	
Baranidharan 2021	One-Year Results of Prospective Research Study Using 10 kHz Spinal Cord Stimulation in Persistent Nonoperated Low Back Pain of Neuropathic Origin: Maiden Back Study	Non-comparative cohort study		×
Dones 2008	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: Commentary	Commentary	×	
Kemler 2010	The cost-effectiveness of spinal cord stimulation for complex regional pain syndrome	Economic analysis performed post hoc and independent of original RCT	×	
Liem 2013	A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain	Non-comparative on/off study	×	
Maclver 2010	The effect of spinal cord stimulation (SCS) on sensory changes in neuropathic pain	Not an RCT		×
Marchand 1991	The effects of dorsal column stimulation on measures of clinical and experimental pain in man	Non-randomised study	×	
Rigoard 2013	Treatment of the back pain component of failed back surgery syndrome (FBSS) by multi-column spinal cord stimulation: A multicentre prospective study	Non-comparative cohort study	×	
Sagher 2008	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: Commentary	Commentary	×	
Steinbach 2017	High-frequency spinal cord stimulation at 10 kHz for the treatment of chronic neuropathic pain after a II-III degree burn	Single case report	×	
Taylor 2005	Spinal cord stimulation for failed back surgery syndrome: A decision-analytic model and cost-effectiveness analysis	Economic analysis developed independent of RCT	×	
Van Beek 2015	Sustained treatment effect of spinal cord stimulation in painful diabetic peripheral Neuropathy: 24-Month Follow-up of a prospective Two-Center randomized controlled trial	Non-comparative cohort from RCT <sup>c</sup>	×	
Veizi 2017 <sup>d</sup>	Spinal Cord Stimulation (SCS) with Anatomically Guided (3D) Neural Targeting Shows Superior Chronic Axial Low Back Pain Relief Compared to Traditional SCS-LUMINA Study	Non-randomised comparative cohort study		×
Winfree 2005	Spinal cord stimulation for the relief of chronic pain	Commentary	×	

Abbreviations: CMM, conventional medical management; DRGS, dorsal root ganglion stimulation; kHz, kilohertz; HF, high frequency; RCT, randomised controlled trial; SCS, spinal cord stimulation; v, versus

**a** This study is actually an on/off study; there is no concurrent comparator group and randomisation was restricted to order of active/inactive intervention phases. Therefore this is a non-comparative study.

**b** Commentary on RCT publication not listed in Cochrane reviews nor in stakeholder submissions: Deer, T., Pope, J., Benyamin, R., et al. (2016). Prospective, multicenter, randomized, double-blinded, partial crossover study to assess the safety and efficacy of the novel neuromodulation system in the treatment of patients with chronic pain of peripheral nerve origin. *Neuromodulation*. 19(1):91-100.

**c** Original RCT randomised 36 patients, with 22 receiving SCS – this is effectively a single cohort study with long-term follow-up of patients who received SCS.

**d** Comparative study with historical controls.

**Table App 10 Additional RCT publications from stakeholder submissions for RCTs included in either of the Cochrane reviews**

RCT identifier	Study ID	Title
NSRBP-RCT	Kallewaard 2022	/ #684 EUROPEAN RANDOMIZED CONTROLLED TRIAL TO STUDY THE EFFECTS OF DIFFERENTIAL TARGET MULTIPLEXED SCS IN TREATING INTRACTABLE CHRONIC BACK PAIN WITHOUT PREVIOUS LUMBAR SPINE SURGERY: TRACK 3: NEUROSTIMULATION FOR BACK AND LEG PAIN
PROCESS	Kumar 2007	Factors affecting spinal cord stimulation outcome in chronic benign pain with suggestions to improve success rate
SENZA-PDN	Petersen 2022	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
	Petersen 2022	Durability of High-Frequency 10-kHz Spinal Cord Stimulation for Patients With Painful Diabetic Neuropathy Refractory to Conventional Treatments: 12-Month Results From a Randomized Controlled Trial

Abbreviations: kHz, kilohertz; RCT, randomised controlled trial; SCS, spinal cord stimulation

**Table App 11 Additional RCT publications from stakeholder submissions for RCTs excluded from either of the Cochrane reviews**

RCT identifier	Study ID	Title
ESTIMET	Rigoard 2021	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)
EVOKE	Mekhail 2022	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
ReActiv8-B NCT02577354	Gilligan 2023	Long-Term Outcomes of Restorative Neurostimulation in Patients With Refractory Chronic Low Back Pain Secondary to Multifidus Dysfunction: Two-Year Results of the ReActiv8-B Pivotal Trial
SENZA-RCT	Kapural 2016	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
	Amirdelfan 2018	Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT
SUNBURST	D'Souza 2021	Neuromodulation With Burst and Tonic Stimulation Decreases Opioid Consumption: A Post Hoc Analysis of the Success Using Neuromodulation With BURST (SUNBURST) Randomized Controlled Trial
	Leong 2021	Potential Therapeutic Effect of Low Amplitude Burst Spinal Cord Stimulation on Pain

Abbreviations: kHz, kilohertz; RCT, randomised controlled trial

**Table App 12 Publications from stakeholder submissions for RCTs not listed in either Cochrane Review**

RCT identifier	Study ID	Title
ACCURATE	Deer 2017	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
	Deer 2019	Comparison of Paresthesia Coverage of Patient's Pain: Dorsal Root Ganglion vs. Spinal Cord Stimulation. An ACCURATE Study Sub-Analysis
	Levy 2020	Therapy Habituation at 12 Months: Spinal Cord Stimulation Versus Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome Type I and II
COMBO	Wallace 2022	ID:16146 Two-Year Outcomes of an SCS System Capable of Multiple Neurostimulation Modalities: A Randomized Controlled Trial
	Wallace 2023	Combination therapy with simultaneous delivery of spinal cord stimulation modalities: COMBO randomized controlled trial
HALO RCT	Breel 2021	A Comparison of 1000 Hz to 30 Hz Spinal Cord Stimulation Strategies in Patients with Unilateral Neuropathic Leg Pain Due to Failed Back Surgery Syndrome: A Multicenter, Randomized, Double-Blinded, Crossover Clinical Study (HALO)

RCT identifier	Study ID	Title
RestoreSensor	Schultz 2012	Sensor-driven position-adaptive spinal cord stimulation for chronic pain
PFNS add-on trial	van Gorp 2019	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
	Van Heteren 2022	SPINAL CORD STIMULATION WITH ADDITIONAL PERIPHERAL NERVE FIELD STIMULATION VERSUS SPINAL CORD STIMULATION ALONE ON BACK PAIN AND QUALITY OF LIFE IN PATIENTS WITH FAILED BACK SURGERY SYNDROME
	van Roosendaal 2023	Subcutaneous Stimulation as Add-on Therapy to Spinal Cord Stimulation in Patients With Persistent Spinal Pain Syndrome Significantly Increases the Total Electrical Charge per Second: Aspects on Stimulation Parameters and Energy Requirements of the Implanted Neurostimulators
SUFR	Bolash 2019	Wireless High-Frequency Spinal Cord Stimulation (10 kHz) Compared with Multiwaveform Low-Frequency Spinal Cord Stimulation in the Management of Chronic Pain in Failed Back Surgery Syndrome Subjects: Preliminary Results of a Multicenter, Prospective Randomized Controlled Study
–	Canós-Verdecho 2021	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
–	Fishman 2021	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

Abbreviations: Hz, hertz; kHz, kilohertz; RCT, randomised controlled trial

**Table App 13 Non-comparative studies from stakeholder submissions (incl. on/off and before/after studies)**

Study ID	Title
Al-Kaisy 2014	Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study
Al-Kaisy 2018	Long-term improvements in chronic axial low back pain patients without previous spinal surgery: A cohort analysis of 10-kHz high-frequency spinal cord stimulation over 36 months
Al-Kaisy 2020	Explant rates of electrical neuromodulation devices in 1177 patients in a single center over an 11-year period
Al-Kaisy 2020	10 kHz spinal cord stimulation for the treatment of non-surgical refractory back pain: subanalysis of pooled data from two prospective studies
Amirdelfan 2020	High-Frequency spinal cord stimulation at 10 kHz for the treatment of combined neck and arm pain: Results from a prospective multicenter study
Benyamin 2020	Options: A prospective, open-label study of high-dose spinal cord stimulation in patients with chronic back and leg pain
Brinzeu 2019	Spinal cord stimulation for chronic refractory pain: Long-term effectiveness and safety data from a multicentre registry
Brooker 2021	ECAP-Controlled Closed-Loop Spinal Cord Stimulation Efficacy and Opioid Reduction Over 24-Months: Final Results of the Prospective, Multicenter, Open-Label Avalon Study
Burgher 2020	Ten kilohertz SCS for treatment of chronic upper extremity pain (UEP): Results from prospective observational study
Chen 2022	A Real-World Analysis of High-Frequency 10 kHz Spinal Cord Stimulation for the Treatment of Painful Diabetic Peripheral Neuropathy
Courtney 2015	Improved pain relief with burst spinal cord stimulation for two weeks in patients using tonic stimulation: Results from a small clinical study
De Jaeger 2020	The added value of high dose spinal cord stimulation in patients with failed back surgery syndrome after conversion from standard spinal cord stimulation
De Jaeger 2021	The Long-Term Response to High-Dose Spinal Cord Stimulation in Patients With Failed Back Surgery Syndrome After Conversion From Standard Spinal Cord Stimulation: An Effectiveness and Prediction Study
De Ridder 2010	Burst spinal cord stimulation: Toward paresthesia-free pain suppression
De Vos 2014	Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy
Deer 2016	Results from the Partnership for Advancement in Neuromodulation Registry: A 24-Month Follow-Up
Deer 2021	Novel Intermittent Dosing Burst Paradigm in Spinal Cord Stimulation
Deer 2022	Ultra-Low Energy Cycled Burst Spinal Cord Stimulation Yields Robust Outcomes in Pain, Function, and Affective Domains: A Subanalysis From Two Prospective, Multicenter, International Clinical Trials
Deer 2022	Passive Recharge Burst Spinal Cord Stimulation Provides Sustainable Improvements in Pain and Psychosocial Function: 2-year Results from the TRIUMPH Study
Do 2021	Real-World Analysis: Long-Term Effect of Spinal Cord Stimulation With Different Waveforms for Patients With Failed Back Surgery Syndrome
El Majdoub 2019	10 kHz cervical SCS for chronic neck and upper limb pain: 12 months' results
Falowski 2021	Improved Psychosocial and Functional Outcomes and Reduced Opioid Usage Following Burst Spinal Cord Stimulation
Fishman 2020	Prospective, Multicenter Feasibility Study to Evaluate Differential Target Multiplexed Spinal Cord Stimulation Programming in Subjects With Chronic Intractable Back Pain With or Without Leg Pain

Study ID	Title
Fishman 2020	Vectors post market study: SCS (HD) trialing duration and 12-month pain relief following trial success
Fraifeld 2021	Systemic Opioid Prescribing Patterns and Total Cost of Care in Patients Initiating Spinal Cord Stimulation Therapy: A Retrospective Analysis
Galan 2020	10-kHz spinal cord stimulation treatment for painful diabetic neuropathy: Results from post-hoc analysis of the SENZA-PPN study
Gatzinsky 2017	Evaluation of the Effectiveness of Percutaneous Octapolar Leads in Pain Treatment with Spinal Cord Stimulation of Patients with Failed Back Surgery Syndrome During a 1-Year Follow-Up: A Prospective Multicenter International Study
Goudman 2021	High-Dose Spinal Cord Stimulation Reduces Long-Term Pain Medication Use in Patients With Failed Back Surgery Syndrome Who Obtained at Least 50% Pain Intensity and Medication Reduction During a Trial Period: A Registry-Based Cohort Study
Gupta 2020	10-kHz Spinal Cord Stimulation for Chronic Postsurgical Pain: Results From a 12-Month Prospective, Multicenter Study
Hagedorn 2021	Antibacterial envelope use for the prevention of surgical site infection in spinal cord stimulator implantation surgery: A retrospective review of 52 cases
Hatheway 2021	Long-Term Efficacy of a Novel Spinal Cord Stimulation Clinical Workflow Using Kilohertz Stimulation: Twelve-Month Results From the Vectors Study
Huygen 2019	Evaluating Dorsal Root Ganglion Stimulation in a Prospective Dutch Cohort
Kallewaard 2021	10 kHz Spinal Cord Stimulation for the Treatment of Failed Back Surgery Syndrome with Predominant Leg Pain: Results from a Prospective Study in Patients from the Dutch Healthcare System
Kinfe 2017	Burst Spinal Cord Stimulation Increases Peripheral Antineuroinflammatory Interleukin 10 Levels in Failed Back Surgery Syndrome Patients With Predominant Back Pain
Manfield 2019	Safety and Utility of Spinal Magnetic Resonance Imaging in Patients with High-Frequency Spinal Cord Stimulators: A Prospective Single-Centre Study
Mekhail 2011	Retrospective Review of 707 Cases of Spinal Cord Stimulation: Indications and Complications
Metzger 2020	Pain relief outcomes using an SCS device capable of delivering combination therapy with advanced waveforms and field shapes
Metzger 2021	A novel fast-acting sub-perception spinal cord stimulation therapy enables rapid onset of analgesia in patients with chronic pain
Moeschler 2015	Spinal Cord Stimulator Explantation for Magnetic Resonance Imaging: A Case Series
Morgalla 2018	Dorsal root ganglion stimulation (DRGS) for the treatment of chronic neuropathic pain: A single-center study with long-term prospective results in 62 cases
Parikh 2021	Comparing effectiveness of standard vs hf10 spinal cord stimulator implants for chronic intractable pain
Paz-Solis 2022	Exploration of High- and Low-Frequency Options for Subperception Spinal Cord Stimulation Using Neural Dosing Parameter Relationships: The HALO Study
Russo 2020	Sustained long-term outcomes with closed-loop spinal cord stimulation: 12-month results of the prospective, multicenter, open-label avalon study
Sayed 2020	Retrospective analysis of real-world outcomes of 10 khz SCS in patients with upper limb and neck pain
Soldati 2002	National Italian Register of implantable systems for spinal cord stimulation (SCS): Analysis of preliminary data
Stauss 2019	A multicenter real-world review of 10 kHz SCS outcomes for treatment of chronic trunk and/or limb pain
Tiede 2013	Novel spinal cord stimulation parameters in patients with predominant back pain
Van Beek 2018	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
Van Buyten 2001	Efficacy of spinal cord stimulation: 10 Years of experience in a pain centre in Belgium
Van Buyten 2003	The Performance and Safety of an Implantable Spinal Cord Stimulation System in Patients with Chronic Pain: A 5-Year Study
Van Buyten 2013	High-frequency spinal cord stimulation for the treatment of chronic back pain patients: Results of a prospective multicenter European clinical study
Van Buyten 2017	Therapy-Related Explants After Spinal Cord Stimulation: Results of an International Retrospective Chart Review Study
Verrills 2019	Dorsal Root Ganglion Stimulation Is Paresthesia-Independent: A Retrospective Study
Wang 2021	Explantation Rates of High Frequency Spinal Cord Stimulation in Two Outpatient Clinics
Zhou 2023	Clinical Effect Analysis of Spinal Cord Electrical Stimulator Implantation for Diabetic Foot

Abbreviations: kHz, kilohertz; SCS, spinal cord stimulation;

**Table App 14 Systematic reviews and meta-analyses from stakeholder submissions**

Study ID	Title
Bala 2008	Systematic review of the (Cost-)effectiveness of spinal cord stimulation for people with failed back surgery syndrome
Baranidharan 2021	Efficacy and Safety of 10 kHz Spinal Cord Stimulation for the Treatment of Chronic Pain: A Systematic Review and Narrative Synthesis of Real-World Retrospective Studies
Baranidharan 2021	Pain Relief and Safety Outcomes with Cervical 10 kHz Spinal Cord Stimulation: Systematic Literature Review and Meta-analysis
Bordeleau 2019	Effects of Tonic Spinal Cord Stimulation on Sensory Perception in Chronic Pain Patients: A Systematic Review

Study ID	Title
Conger 2020	The effectiveness of spinal cord stimulation for the treatment of axial low back pain: A systematic review with narrative synthesis
Deer 2020	A systematic literature review of spine neurostimulation therapies for the treatment of pain
Duarte 2022	Systematic Review and Network Meta-analysis of Neurostimulation for Painful Diabetic Neuropathy
Frey 2009	Spinal cord stimulation for patients with failed back surgery syndrome: A systematic review
Grider 2016	Effectiveness of spinal cord stimulation in chronic spinal pain: A systematic review
Hoelzer 2022	Indirect Comparison of 10 kHz Spinal Cord Stimulation (SCS) versus Traditional Low-Frequency SCS for the Treatment of Painful Diabetic Neuropathy: A Systematic Review of Randomized Controlled Trials
Hornberger 2008	Rechargeable spinal cord stimulation versus non-rechargeable system for patients with failed back surgery syndrome: a cost-consequences analysis
Luecke 2021	Spinal cord stimulation: a real-world data analysis on outcomes and differences between rechargeable and non-rechargeable implantable pulse generators
Odonkor 2019	Spinal Cord Stimulation vs Conventional Therapies for the Treatment of Chronic Low Back and Leg Pain: A Systematic Review of Health Care Resource Utilization and Outcomes in the Last Decade
Pollard 2019	The effect of spinal cord stimulation on pain medication reduction in intractable spine and limb pain: A systematic review of randomized controlled trials and meta-analysis
Slavin 2013	Treatment of chronic, intractable pain with a conventional implantable pulse generator: A meta-analysis of 4 clinical studies
Taylor 2004	The cost effectiveness of spinal cord stimulation in the treatment of pain: A systematic review of the literature
Taylor 2005	Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: A systematic review and analysis of prognostic factors

Abbreviations: kHz, kilohertz; SCS, spinal cord stimulation

**Table App 15 Safety studies from stakeholder submissions**

Study ID	Title
Cameron 2004	Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: A 20-year literature review
Eldabe 2016	Complications of spinal cord stimulation and peripheral nerve stimulation techniques: A review of the literature
Hayek 2015	Treatment-limiting complications of percutaneous spinal cord stimulator implants: A review of eight years of experience from an academic center database
Jones 2022	Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration
Kable 2002	Adverse events in surgical patients in Australia
Levy 2011	Incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads
Quigley 2003	Long-Term Outcome of Spinal Cord Stimulation and Hardware Complications
Rauk 2023	Long-term safety of spinal cord stimulation systems in a prospective, global registry of patients with chronic pain

**Table App 16 Economic studies from stakeholder submissions**

Study ID	Title
Costandi 2020	Longevity and Utilization Cost of Rechargeable and Non-Rechargeable Spinal Cord Stimulation Implants: A Comparative Study
Deloitte Access Economics Australia 2019	Cost effectiveness of pain devices
Farber 2017	Long-term cost-utility of spinal cord stimulation in patients with failed back surgery syndrome
Farber 2017	Increasing rates of imaging in failed back surgery syndrome patients: Implications for spinal cord stimulation
Hollingworth 2011	Costs and cost-effectiveness of spinal cord stimulation (SCS) for failed back surgery syndrome: An observational study in a workers compensation population
KPMG 2022	An analysis of the service cost of Spinal Cord Stimulator (SCS) services
Kumar 2009	Financial impact of spinal cord stimulation on the healthcare budget: A comparative analysis of costs in Canada and the United States
Kumar 2013	Cost-effectiveness of spinal cord stimulation therapy in management of chronic pain
Lad 2016	Longer Delay From Chronic Pain to Spinal Cord Stimulation Results in Higher Healthcare Resource Utilization
McClure 2021	A Systematic Review of the Cost-Utility of Spinal Cord Stimulation for Persistent Low Back Pain in Patients With Failed Back Surgery Syndrome

Study ID	Title
Mekhail 2021	Cost-Effectiveness of Dorsal Root Ganglion Stimulation or Spinal Cord Stimulation for Complex Regional Pain Syndrome
Niyomsri 2020	A Systematic Review of Economic Evaluations Reporting the Cost-Effectiveness of Spinal Cord Stimulation
North 2007	Spinal cord stimulation versus reoperation for failed back surgery syndrome: A cost effectiveness and cost utility analysis based on a randomized, controlled trial
Patel 2022	Cost-effectiveness of 10-kHz spinal cord stimulation therapy compared with conventional medical management over the first 12 months of therapy for patients with nonsurgical back pain: randomized controlled trial
Rajkumar 2022	Health Care Economics of High-Frequency Spinal Cord Stimulation for Painful Diabetic Peripheral Neuropathy
Rajkumar 2023	Health Care Resource Utilization of High-Frequency Spinal Cord Stimulation for Treatment of Chronic Refractory Low Back Pain
Rojo 2021	Real-world cost-effectiveness analysis of spinal cord stimulation vs conventional therapy in the management of failed back surgery syndrome
Simpson 2009	Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: Systematic review and economic evaluation
Taylor 2010	The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome
Taylor 2020	High-frequency 10 kHz Spinal Cord Stimulation for Chronic Back and Leg Pain: Cost-consequence and Cost-effectiveness Analyses
Verrills 2016	A review of spinal cord stimulation systems for chronic pain
Weinand 2022	Pain Therapy With Spinal Cord Stimulation (SCS) in Patients With Painful Diabetic Neuropathy (PDN): Results of a Budget Impact Model
Zucco 2015	Cost-Effectiveness and Cost-Utility Analysis of Spinal Cord Stimulation in Patients With Failed Back Surgery Syndrome: Results From the PRECISE Study

Abbreviations: kHz, kilohertz

**Table App 17 Clinical longevity study from stakeholder submissions**

Study ID	Title
Deer 2023	Clinical Longevity of 106,462 Rechargeable and Primary Cell Spinal Cord Stimulators: Real World Study in the Medicare Population

**Table App 18 Study predicting impact on access to MRI from stakeholder submissions**

Study ID	Title
Desai 2015	The rate of magnetic resonance imaging in patients with spinal cord stimulation

**Table App 19 Patient selection studies from stakeholder submissions**

Study ID	Title
Goudman 2022	Patient Selection for Spinal Cord Stimulation in Treatment of Pain: Sequential Decision-Making Model — A Narrative Review
Gould 2021	Psychosocial characteristics of candidates for implantable pain devices: Validation of an assessment model
Grinberg 2019	A revised psychosocial assessment model for implantable pain devices to improve their evidence basis and consensus with updated pain management guidelines
Thomson 2020	Appropriate referral and selection of patients with chronic pain for spinal cord stimulation: European consensus recommendations and e-health tool

**Table App 20 SCS technical studies from stakeholder submissions**

Study ID	Title
Al-Kaisy 2020	Comparison of Paresthesia Mapping to Anatomical Placement in Burst Spinal Cord Stimulation: Initial Trial Results of the Prospective, Multicenter, Randomized, Double-Blinded, Crossover, CRISP Study
Al-Kaisy 2022	Comparison of Paresthesia Mapping With Anatomic Placement in Burst Spinal Cord Stimulation: Long-Term Results of the Prospective, Multicenter, Randomized, Double-Blind, Crossover CRISP Study
Chakravarthy 2020	Sensing evoked compound action potentials from the spinal cord: Novel preclinical and clinical considerations for the pain management researcher and clinician



Study ID	Title
Chakravarthy 2022	A Clinical Feasibility Study of Spinal Evoked Compound Action Potential Estimation Methods
De Carolis 2017	Paresthesia-independence: An assessment of technical factors related to 10 kHz paresthesia-free spinal cord stimulation
El-Naggar 2021	Using Lower Amplitudes to Maintain Effective High Dose Spinal Cord Stimulation Therapy (SCS Dosing Pilot Study)
Pilitsis 2021	The Evoked Compound Action Potential as a Predictor for Perception in Chronic Pain Patients: Tools for Automatic Spinal Cord Stimulator Programming and Control
Pope 2020	Anatomic Lead Placement Without Paresthesia Mapping Provides Effective and Predictable Therapy During the Trial Evaluation Period: Results From the Prospective, Multicenter, Randomized, DELIVERY Study
Vallejo 2021	A New Direction for Closed-Loop Spinal Cord Stimulation: Combining Contemporary Therapy Paradigms with Evoked Compound Action Potential Sensing

Abbreviations: kHz, kilohertz

**Table App 21 Critiques and position statement from stakeholder submissions**

Study ID	Title
Deer 2023	Serious Issues in Authorship, Design, and Conclusions of JAMA Neurology Real-World Evidence Study on Spinal Cord Stimulation Outcomes and Costs as Compared to Conventional Medical Therapy
Russo 2022	Response to Recent JAMA Article on Spinal Cord Stimulation
Sullivan 2023	Spinal Cord Stimulator Complications Reported to the Australian Therapeutic Goods Administration

Abbreviations: JAMA, the Journal of the American Medical Association

## C.2 Comparative cost-effectiveness

### C.2.1 Search strings

Following an initial scoping search, the primary search was conducted on 06 February 2023 in EMBASE.com using the search string detailed in Table App 22.

**Table App 22 Search strings for cost-effectiveness search**

Query no.	Search string (EMBASE.com)
#1	'spinal cord stimulation'/exp
#2	((('spinal cord') NEAR/3 (stimulat* OR electrostimulat* OR neurostim* OR neuromodulat*)):ti,ab,kw OR (('dorsal root' OR 'dorsal root ganglion') NEAR/3 (stimulat* OR electrostimulat* OR neurostim* OR neuromodulat*)):ti,ab,kw
#3	'economic evaluation'/exp OR 'health care cost'/de OR 'economic model'/exp OR 'health utility'/de OR 'economics'/de
#4	((('cost* OR economic OR markov') NEAR/3 (model OR analysis OR analyses)):ti,ab,kw) OR 'cost impact\$':ti,ab,kw OR 'economic impact\$':ti,ab,kw OR 'cost outcome\$':ti,ab,kw OR 'budget impact\$':ti,ab,kw
#5	'life year\$':ti,ab,kw OR qaly\$':ti,ab,kw
#6	#1 OR #2
#7	#3 OR #4 OR #5
#8	#6 AND #7
#9	#8 NOT ([conference abstract]/lim OR [conference review]/lim OR [letter]/lim OR [editorial]/lim)

A total of 620 results identified in the literature search were downloaded into an Endnote database for de-duplication. Unique records were then screened for inclusion and underwent informal critical appraisal. The reference lists of included studies were also scanned for any additional relevant studies that might not have been identified in the formal literature search.

### C.2.2 Included studies

A total of 118 studies were identified in the literature searches for screening. Studies provided in stakeholder submissions (Table App 16) were also screened using the same criteria. One SR that assessed economic evaluations of SCS and DRGS for the management a number of chronic pain conditions was

retrieved (Niyomsri 2020). A more recent SR was identified (McClure 2021); however, this was excluded because it only reported on patients with FBSS. A further SR (Bala 2008) was identified but excluded as the Niyomsri (2020) SR was more recent.

All included studies from the search were checked for inclusion in Niyomsri (2020). One study (Rojo 2021) that was beyond the search date range of the Niyomsri SR was added to supplement the findings of the SR. The report authored by Deloitte (for the NSANZ, dated March 2019) was also used to supplement data from the included studies.

The report authored by KPMG (for the MTAA, dated March 2022) was excluded as it presented a cost analysis only.

Other publications were excluded due to:

- incorrect comparison (for example, rechargeable v non-rechargeable devices, or comparison of pre- and post-treatment values in a single arm)
- non-comparative study (SCS only)
- cost analysis without cost-effectiveness outcomes.

Two articles appeared to be eligible for inclusion (Mekhail 2021; Patel 2022) but were excluded on full text review:

- Patel (2022) was found to have employed a cross-over design that resulted in almost all comparator patients being switched to SCS at 6 months. The cross-over occurred 18 months prior to the collection of data for the primary endpoint, thus rendering the outcome unusable and the article was excluded.
- Mekhail (2021) ostensibly presented a three-way comparison of DRGS, SCS and CMM but the values for the CMM 'arm' were derived from pre-treatment values for the treated patients and did not represent a legitimate comparison. This was treated as a longitudinal study and excluded.

## Appendix D Data extraction

### D.1 Included systematic reviews on comparative effectiveness

**Table App 23 Summary of key systematic reviews**

Study ID	Research questions	Search dates and inclusion/exclusion criteria	Results	Authors' conclusions
Traegar (2023)	To assess the effects, including benefits and harms, of SCS for people with low back pain.	<p>Inception to 10 June 2022</p> <p><b>Inclusion:</b> RCTs; quasi-randomised trials; cross-over trials; participants <math>\geq 18</math> yrs of any gender with chronic low back pain (&gt; 12 wks' pain duration) with or without leg pain and including people with FBSS; studies that compared SCS to placebo or no treatment or assessed SCS as an addition to CMM; studies with SCS procedures of any kind</p> <p><b>Exclusion:</b> Participants with pain conditions other than chronic low back pain, with or without leg pain, unless separate data could be obtained for participants with chronic low back pain; participants with chronic low back pain caused by serious spinal pathology; studies comparing SCS to very low amplitude stimulation</p>	<p><b>SCS versus placebo</b></p> <p><b>Medium-term outcomes</b></p> <p><i>Pain intensity (VAS)</i>  <b>SCS:</b> Mean back pain was 4 points better (8.2 points better to 0.2 points worse) (1 study, N=50)  <b>Placebo:</b> Mean back pain was 61 points (1 study, N=50)</p> <p><i>Function</i>  <b>SCS:</b> Mean disability was 1.3 points better (3.9 points better to 1.3 points worse) (1 study, N=50)  <b>Placebo:</b> Mean disability was 35.4 points (1 study, N=50)</p> <p><i>HRQoL</i>  <b>SCS:</b> Mean QoL was 0.04 points better (0.16 points better to 0.08 points worse) (1 study, N=50)  <b>Placebo:</b> Mean QoL was 0.44 points out of 1</p> <p><i>Global assessment of efficacy</i>            No data available (0 studies)</p> <p><i>AEs</i>            No data available (0 studies)</p> <p><b>SCS + CMM versus CMM alone</b></p> <p><b>Medium-term outcomes</b></p> <p><i>Low back pain:</i> Mean pain was 26 points better with the addition SCS (95% CI 56.2 points better to 42 points worse, <math>I^2=98\%</math>) (3 studies, N=430)  <i>Leg pain:</i> Mean leg pain intensity was 18.8 points better with the addition of SCS (95% CI 33.2 points better to 4.5 points better, <math>I^2=82\%</math>) (2 studies, N=290)  <i>Function:</i> Mean function was 16.2 points better with the addition of SCS (95% CI 19.4 points better to 13.0 points better, <math>I^2=95\%</math>) (3 studies, N=430)  <i>HRQoL:</i> Mean HRQoL was 7.6 points better with SCS (95% CI 15.8 points better to 0.6 points worse, <math>I^2=53\%</math>) (2 studies, N=289)  <i>Global assessment of efficacy (<math>\geq 50\%</math> better):</i> Participants receiving SCS 7.4 times more likely to report 50% or better improvement in pain (95% CI 23.4 times more likely to 2.3 times more likely, <math>I^2=70\%</math>) (3 studies, N=430)  <i>Withdrawals due to AEs:</i> 2/30 in HF-SCS group compared to 0/76 control group (1 study, N=159)  <i>AEs:</i> 65/157 (41.4%) SCS + CMM group compared to 49/179 (27.4%) CMM alone (RR 2.32, 95% CI 0.39 to 13.79. <math>I^2=90\%</math>) (2 studies, N=336)  <i>SAEs:</i> 6/65 HF-SCS group compared to 4/75 control group (RR 1.73, 95% CI 0.51 to 5.87,</p>	Data in this review does not support the use of SCS to manage low back pain outside a clinical trial. Current evidence suggests SCS probably does not have sustained clinical benefits that would outweigh the costs and risks of this surgical intervention

Study ID	Research questions	Search dates and inclusion/exclusion criteria	Results	Authors' conclusions
			<p><math>I^2=0\%</math> (1 study, N=140)  <i>Medication use:</i> Opioid medicines 15% lower with SCS (95% CI 27% lower to 0% lower, <math>I^2=0\%</math>) (2 studies, N=290). Daily MMEs 9.4 points lower with SCS (95% CI 19.9 points lower to 1.2 points higher; <math>I^2=0\%</math>) (3 studies, N=430)  <i>Number returning to work:</i> 4/52 SCS group compared to 1/48 control group (RR 3.7, 95% CI 0.4 to 31.9) (1 study, N=100)  <i>Health care use:</i> NR  <u>Long-term outcomes</u>  <i>Low back pain:</i> NR  <i>Leg pain:</i> NR  <i>Function:</i> NR  <i>Global assessment of efficacy (<math>\geq 50\%</math> better):</i> 17/52 participants in SCS group achieved 50% or better improvement compared with 48 participants in the CMM group (RR 1.96, 95% CI 0.93 to 4.12) (1 study, 52 participants)  <i>Withdrawals due to AE:</i> NR  <i>AEs:</i> Proportion of participants not reported (1 study, 84 participants)  <i>SAEs:</i> Proportion of participants not reported (1 study, 84 participants)  <i>Medication use:</i> NR  <i>Number returning to work:</i> NR  <i>Health care use:</i> NR</p>	
O'Connell (2021)	What are the benefits and risks of electrical spinal cord and dorsal root ganglion stimulation for the treatment of chronic pain in adults?	<p>October 2020 and updated in September 2021  <u>Inclusion:</u> RCTs comparing SCS interventions with placebo (sham) stimulation, no treatment or usual care, or comparing SCS interventions + another treatment verses that treatment alone.  Participants <math>\geq 18</math> yrs old with non-cancer and non-ischaeamic pain of <math>&gt;3</math> mo durations  <u>Exclusion:</u> Patients with cancer, ischaemic-related pain, headache of any origin, studies with average baseline (pre-intervention) pain intensity levels <math>&lt;4/10</math> or <math>40/100</math></p>	<p><b>SCS + other intervention vs other intervention alone</b>  <b>Medium and long-term outcomes only</b>  <u>Pain intensity (continuous outcomes)</u>  Medium term: MD -31.22 (95% CI -47 to 34 to -15.10, <math>P &lt; 0.001</math>, <math>I^2 = 95\%</math>) (5 studies, N=635)  Long term: MD -7 (95% CI -24.76 to 10.76, <math>P = 0.44</math>) (1 study, N=44)  <u>Pain intensity (proportion with <math>\geq 50\%</math> pain relief)</u>  Medium term: RR 7.08 (95% CI 3.40 to 14.71, <math>P &lt; 0.001</math>, <math>I^2 = 43\%</math>); RD 0.43 (95% CI 0.14 to 0.73); NNTB 2.3 (95% CI 1.4 to 7.7) (5 studies, N=597)  Long term: RR 15.15 (95% CI 2.11 to 108.91, <math>P = 0.007</math>); RD 0.35 (95% CI 0.2 to 0.49); NNTB 2.86 (95% CI 2.04 to 5) (1 study, N=87)  <u>AEs</u>  Inconsistently reported in the trials.  Medium term:  Lead failure: RD 0.04 (95% CI -0.04 to 0.11, <math>P = 0.31</math>, <math>I^2 = 64\%</math>) (3 studies, N=330)  Infections: RD 0.04 (95% CI 0.01 to 0.07, <math>P = 0.003</math>, <math>I^2 0\%</math>); NNTH 25 (95% CI 14.29 to 100) (4 studies, N=548)  Repeated implantation/reoperation: RD 0.11 (95% CI 0.02 to 0.21, <math>P = 0.02</math>, <math>I^2 = 86\%</math>); NNTH 9.1 (95% CI 4.8 to 50) (4 studies, N=548)  Long term:  Lead repositioning/replacement RD 0.55 (95% CI 0.35 to 0.75, <math>P &lt; 0.001</math>); NNTH 1.8 (95% CI 1.3 to 2.9) (1 study, N=44)</p>	<p>We found very low-certainty evidence that SCS may not provide clinically important benefits on pain intensity compared to placebo stimulation. We found low- to very low-certainty evidence that SCS interventions may provide clinically important benefits for pain intensity when added to conventional medical management or physical therapy. SCS is associated with complications including infection, electrode lead migration/failure and a need for reoperation/re-implantation. The level of certainty regarding the size of those risks is very low. SCS may lead to serious AEs, including death. No evidence was found to support or refute the use of DRGs for chronic pain.</p>

Study ID	Research questions	Search dates and inclusion/exclusion criteria	Results	Authors' conclusions
			<p>Repeated implantation/reoperation: RD 0.94 (95% CI 0.80 to 1.07, P &lt; 0.001); NNTH of 1.05 (95% CI 0.93 to 1.25) (1 study, N=44)</p> <p><u>Secondary outcomes</u></p> <p><u>Disability</u></p> <p>Medium term: MD -15.93 (95% CI -35.99 to 4.13, P = 0.12, I<sup>2</sup> 92%) (2 studies, N=312)</p> <p><u>HRQoL</u></p> <p>Medium term: SMD 0.73 (95% CI 0.46 to 0.99, P &lt; 0.001, I<sup>2</sup> = 54%) (5 studies, N=595)</p> <p>Long term: MD -0.09 (95% CI -0.74 to 0.56) (1 study, N=44)</p> <p><u>Medication use</u></p> <p>Medium term: analgesic use (2 studies, N=154)</p> <p>Opioids RR 0.77 (95% CI 0.58 to 1.01, P = 0.06, I<sup>2</sup> 0%)</p> <p>NSAIDs RR 0.69 (95% CI 0.43 to 1.09, P = 0.11, I<sup>2</sup> 0%)</p> <p>Antidepressants RR 0.68 (95% CI 0.46 to 1.00, P = 0.05, I<sup>2</sup> 0%)</p> <p>Anticonvulsants RR 0.80 (95% CI 0.33 to 1.94, P = 0.62, I<sup>2</sup> 75%)</p> <p>Paracetamol RR 0.58 (95% CI 0.23 to 1.51, P = 0.27) (1 study, N=60)</p>	
NICE 2008	<ul style="list-style-type: none"> <li>To evaluate the clinical effectiveness and side-effects of SCS in terms of pain, health-related quality of life and physical and functional abilities;</li> <li>To estimate the incremental cost-effectiveness of SCS compared with current standard therapy;</li> <li>To estimate the potential overall cost to the NHS in England and Wales.</li> </ul>	<p>To September 2007</p> <p><u>Inclusion:</u> RCTs of SCS in patients with chronic ischaemic pain</p>	<p><b>CLI</b></p> <p><u>Pain</u></p> <p>Non-significant at 6, 12 and 24 months (1 study)</p> <p><u>Limb survival</u></p> <p>Non-significant relative risk of amputation at 18 months of 0.80 (95%CI 0.60 to 1.06) (risk difference -0.07 (95%CI -0.17 to 0.03) for SCS with reference to control) (4 studies)</p> <p><u>HRQoL</u></p> <p>Non-significant difference at 6 and 18 months (1 trial)</p> <p><b>Angina</b></p> <p><u>Pain</u></p> <p>Non-significant difference at 6-weeks (1 trial)</p> <p><u>Angina attacks</u></p> <p>Significantly reduced frequency of angina attacks in the SCS group compared with the no SCS group (p&lt;0.05) at 6-8 weeks (deJongste), and the SCS compared with inactive stimulator at 6 weeks (p=0.01) (Hautvast). No difference between treatment groups, with a significant reduction in angina attacks for both the SCS and CABG groups at 6 months (ESBY).</p> <p>Exercise testing of time to angina was significantly more improved in SCS than no SCS group (p&lt;0.05) (deJongste), and in SCS than inactive stimulator (p=0.01) (Hautvast), and in SCS than PMR at 3 months (p=0.028) although not significantly different at 12 months (SPIRIT).</p> <p><u>HRQoL</u></p> <p>No significant difference between SCS and comparator (4 trials)</p>	<p>Trial evidence failed to demonstrate that pain relief in CLI was better for SCS than for CMM. Trial evidence suggested that SCS was effective in delaying angina pain onset during exercise at short-term follow-up, though not more so than coronary artery bypass grafting for those patients eligible for that surgery, although SCS was a relatively safe alternative to CABG.</p> <p>Spinal cord stimulation is not recommended as a treatment option for adults with chronic pain of ischaemic origin except in the context of research as part of a clinical trial. Such research should be designed to generate robust evidence about the benefits of spinal cord stimulation (including pain relief, functional outcomes and quality of life) compared with standard care.</p>

Abbreviations: AEs, adverse events; CABG; coronary artery bypass grafting; CI, confidence interval; CLI, critical limb ischaemia; CMM, conventional medical management; DRGS, dorsal root ganglion stimulation; FBSS, failed back surgery syndrome; HF, high-frequency; HRQoL, health-related quality of life; MD, mean difference; MMEs, morphine equivalents; mo, months; N, population; NHS, National Health Service; NNTH, number needed to treat for an additional beneficial outcome; NNTH, number needed to treat for an additional harmful outcome; NSAIDs, non-steroidal anti-inflammatory drugs; PMR, polymyalgia rheumatica; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio; SCS, spinal cord stimulation; VAS, visual analogue scale; wks, weeks; yrs, years

## Appendix E Patient selection and management

### E.1 Included publications

**Table App 24 Summary of included publications for patient selection and management**

Developer (Year) Country	Title Industry funding	Treatment Population	Recommendation type Development methodology	Recommendation category in report
ASPN (2022) (Sayed 2022) USA	The American Society of Pain and Neuroscience (ASPN) evidence-based clinical guideline of interventional treatments for low back pain <i>No industry funding</i>	Suite of treatment options including SCS LBP	Evidence-based Recommendations from the ASPN Back Group (a multidisciplinary group of physicians). A literature search identified peer-reviewed literature that was critiqued using USPSTF criteria for quality of evidence, with modifications for interventional pain studies. RCT evidence was considered the highest quality of evidence.	5.2.1 Clinical indications Additional indications
Ziegler (2022) <sup>a</sup> Germany	Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: International expert consensus recommendations <i>Sponsored by Worwag Pharma</i>	Suite of treatment options including SCS Diabetic sensorimotor polyneuropathy	Evidence-informed Recommendations from a panel of 14 diabetologists and 1 neurologist. Consensus recommendations were made from published data, where available, and using the participating experts' own clinical experience where evidence from clinical trials was lacking. Hierarchical approach considering evidence from systematic reviews, meta-analyses, single RCTs. The Delphi method was used to reach a consensus.	Additional indications
Dutch Consensus (Edelbroek 2022) The Netherlands	Dutch Consensus Paper: A consensus view on the place of neurostimulation within the treatment arsenal of five reimbursed indications for neurostimulation in The Netherlands <i>No industry funding</i>	Neurostimulation (SCS, DRGS, ONS) PSPS type 2 with arm or leg pain, CRPS, PDPN, other SFNs, medically refractory chronic cluster headache	Consensus-based Recommendations from a multidisciplinary scientific committee. A narrative literature review and expert opinions were used to form a minimum of conservative treatments	5.2.1 Clinical indications 5.2.2 Eligibility criteria
NACC (2022) (Deer 2022) USA	The Neurostimulation Appropriateness Consensus Committee (NACC): Recommendations on best practices for cervical neurostimulation <i>Funded by the INS</i>	Cervical SCS, cervical DRGS Pain syndromes	Evidence-based A literature search was conducted from the last NACC published guidelines (2017) A literature search identified peer-reviewed literature that was critiqued using USPSTF criteria for quality of evidence, with modifications for neurostimulation studies. Recommendations were based on the strength of evidence (high, moderate low) or consensus when evidence was scant.	Additional indications 5.3.2 Trial stimulation
FDA (2020) USA	Conduct a trial stimulation period before implanting a spinal cord stimulator (SCS) <i>NR</i>	SCS Chronic pain of the trunk and limbs	Regulatory advice The FDA recently reviewed the MDRs received between 27 July 2016 and 27 July 2020 associated with SCS devices intended for pain.	5.3.2 Trial stimulation

Developer (Year) Country	Title Industry funding	Treatment Population	Recommendation type Development methodology	Recommendation category in report
Bates (2019) Australia	A comprehensive algorithm for management of neuropathic pain <i>Funded by Abbott</i>	SCS Neuropathic pain	Adaptations from recommendations All guidelines focused on the assessment of neuropathic pain.	5.3 Management pathways
NACC (2019) (Deer 2019) USA	The Neuromodulation Appropriateness Consensus Committee on best practices for dorsal root ganglion stimulation <i>Funded by the INS</i>	DRGS CRPS, DPN, other peripheral neuropathies, post-surgical pain, pelvic pain, groin pain, phantom limb and stump pain, postherpetic neuralgia	Evidence-based Recommendations from an international multidisciplinary panel of experts. A comprehensive literature search and systematic evaluation of evidence identified studies that were critiqued using modified Pain Physician criteria and USPSTF criteria for quality of evidence.	5.2.1 Clinical indications 5.2.2 Eligibility criteria 5.2.3 Patients unsuitable for spinal cord stimulation 5.3.1 Types of spinal cord stimulation 5.3.2 Trial stimulation
NICE (2019) UK	Senza spinal cord stimulation system for delivering HF10 therapy to treat chronic neuropathic pain <i>UK Government</i>	Senza HF10 SCS system Chronic neuropathic pain	Evidence-based A comprehensive literature review to identify the highest quality available published evidence relating to the clinical effectiveness of the medical technology. Economic analyses were performed to model cost-effectiveness and cost-utility. Critical appraisal of the evidence using an assessment form suitable for the type of evidence. Consideration by a multidisciplinary panel and broad consultation.	5.3.1 Types of spinal cord stimulation
SIGN (2018) UK	Management of stable angina <i>Scottish Government</i>	Suite of treatment options including SCS Stable angina	Evidence-based Recommendations from a multidisciplinary group of healthcare professionals. Standard systematic review of the evidence.	5.2.3 Patients unsuitable for spinal cord stimulation
EAN (2016) (Crucchi 2016) Europe	EAN guidelines on central neurostimulation therapy in chronic pain conditions <i>Funded by EFNS-EAN</i>	Neurostimulation including SCS Chronic pain conditions	Evidence-based A systematic review and meta-analysis of trials published was conducted. GRADE was used to assess quality of evidence and propose recommendations.	5.2.1 Clinical indications 5.2.2 Eligibility criteria
NACC (2014) (Deer 2014) USA	The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: The Neuromodulation Appropriateness Consensus Committee <i>NR</i>	SCS, DRGS, PNS Chronic pain and ischaemic diseases	Evidence-based A literature search identified Practice Parameters for the use of SCS in the treatment of neuropathic pain, systematic reviews, and prospective trials and RCTs. USPSTF criteria was used to assess quality of the evidence. Clinical experience and expert opinion were used when literature was lacking.	5.2.1 Clinical indications Additional indications 5.2.3 Patients unsuitable for spinal cord stimulation 5.3 Management pathways 5.3.1 Types of spinal cord stimulation 5.3.2 Trial stimulation

Developer (Year) Country	Title Industry funding	Treatment Population	Recommendation type Development methodology	Recommendation category in report
ASIPP IPM Guidelines (2013) ( <i>Manchikanti 2013</i> ) USA	An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations <i>No industry funding</i>	Suite of treatment options including SCS Chronic spinal pain	Evidence-based Systematic review and meta-analysis of evidence. Assessment of evidence was conducted using USPSTF criteria.	5.2.1 Clinical indications 5.2.2 Eligibility criteria
NICE (2008 – <i>considered for review in 2014 and moved to 'static guidance list'</i> ) UK	Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin <i>UK Government</i>	SCS Chronic pain of neuropathic or ischaemic origin	Evidence-based A systematic review of literature with medical or treatment appropriate to condition as the comparator. Economic analyses were performed to model cost-effectiveness and cost-utility. Quality of studies was assessed according to criteria based on NHS CRD report No.4	5.2.1 Clinical indications 5.2.2 Eligibility criteria 5.2.3 Patients unsuitable for spinal cord stimulation 5.3 Management pathways 5.3.2 Trial stimulation

Abbreviations: ASPN, American Society of Pain and Neuroscience; ASIPP, American Society of Interventional Pain Physicians; CRPS, complex regional pain syndrome; DPN, diabetic peripheral neuropathy; DRGS, dorsal root ganglion stimulation; EAN, European Academy of Neurology; EFNS, European Federation of Neurological Societies; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; HF, high-frequency; HRQoL, health-related quality of life; INS, International Neuromodulation Society; IPM, Interventional Pain Management; LBP, low back pain; MDR, Medical Device Reports; NACC, Neuromodulation Appropriateness Consensus Committee/ the Neurostimulation Appropriateness Consensus Committee; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; ONS, occipital nerve stimulation; PDPN, painful diabetic polyneuropathy; PNS, peripheral nerve stimulation; PSPS, persistent spinal pain; RCT, randomised controlled trial; SCS, spinal cord stimulation; SFN, small fibre neuropathies; SIGN, Scottish Intercollegiate Guidelines Network; USPSTF, United States Preventive Services Task Force.

**a** Report originated from an International Consensus Conference on diagnosis and treatment of diabetic sensorimotor polyneuropathy in clinical practice



## E.2 SCS device indications and patient populations

**Table App 25 Device clinical indications and patient populations for SCS systems**

Billing Code	Sponsor	Device name	Clinical indication/patient population
BS322	Boston Scientific	Precision Novi IPG	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 LBP and leg pain
BS383	Boston Scientific	WaveWriter Alpha	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 LBP and leg pain
SJ379	Abbott Medical	Proclaim IPG	Chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS and intractable low back and leg pain
SJ432	Abbott Medical	Proclaim XR IPG	Chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS and intractable low back and leg pain
MI135	Medtronic	PrimeAdvanced Surescan MRI Neurostimulator	Chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain
MI132	Medtronic	RestoreSensor Surescan MRI Neurostimulator	Chronic, intractable pain of the trunk and/or limbs — including unilateral or bilateral pain associated with the following conditions: 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, DDD/herniated disk pain refractory to conservative and surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, CRPS, RSD, or causalgia
MI274	Medtronic	Intellis AdaptiveStim Neurostimulator	Chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain
UY003	Saluda	Evoke Closed Loop Stimulator (CLS)	Chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS, intractable LBP and leg pain
BS254	Boston Scientific	Precision Spectra IPG	Chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS, intractable low back and leg pain
BS362	Boston Scientific	Precision Spectra WaveWriter IPG	Chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS, intractable low back and leg pain
BS389	Boston Scientific	WaveWriter Alpha	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 LBP and leg pain
BS330	Boston Scientific	Precision Montage MRI IPG	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 LBP and leg pain
SJ374	Abbott Medical	Prodigy IPG	Chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: FBSS and intractable low back and leg pain
MI275	Medtronic	Intellis Neurostimulator	Chronic, intractable pain of the trunk and/or limbs, peripheral vascular disease, or intractable angina pectoris
ER496	Emergo Asia	Senza II IPG Kit	Chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with FBSS, intractable LBP, upper back pain, leg pain, upper limb and neck pain
ER535	Emergo Asia	Senza Omnia IPG Kit	Chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with FBSS, intractable LBP, upper back pain, leg pain, upper limb and neck pain

Billing Code	Sponsor	Device name	Clinical indication/patient population
MI495	Medtronic	Vanta™ Recharge-Free Neurostimulator	Chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain

Source: Clinical indications and patient populations derived from IFUs and device webpages; Billing Code information derived from November 2022 PL

Abbreviations: CPRS, complex regional pain syndrome; DDD, degenerative disk disease; FBSS, failed back surgery syndrome; LBP, low back pain; RSD, reflex sympathetic dystrophy.